THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

FEBRUARY, 1941

ORIGINAL ARTICLES.

BLOOD PRESSURE DETERMINATIONS BY PATIENTS WITH ESSENTIAL HYPERTENSION:

II. THE DIFFERENCE BETWEEN HOME AND CLINIC READINGS DURING AND AFTER TREATMENT.*

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In an earlier paper[1a] it was shown that the blood pressure in untreated patients with essential hypertension is often considerably lower in the home than in the office or clinic. Consequently it was decided to re-evaluate the effects of the common forms of therapy by recording blood pressure measurements obtained during therapy in the home as well as in the clinic. In the present discussion the need for and the advantages of this approach in evaluating therapy will be emphasized; detailed results in each of a large number of different forms of treatment will be presented in the subsequent communications.

Material and Methods. The responses to therapy of all of 34 hypertensive patients previously described were studied, using the same method of home and clinic blood pressure study. In all cases the clinic blood pressure was well above 160 systolic and 100 diastolic, the renal function was good, and there was no evidence of heart failure. The ocular fundi showed moderate to marked narrowing of the arterioles in all, with, in addition, choking of the discs in 2 instances.

In 13 of the 34 cases the blood pressure was taken by the patients themselves, while in the remaining 21 the blood pressure was taken by some member of the household. It is essential to stress again the fact that the

* Aided by a grant from the Charlton Fund, Tufts Medical School.

determination of the blood pressure at home was done accurately and without upsetting the patient. The accuracy of the home readings was checked as previously outlined.[1a]

Drugs used included sedatives, nitrites, potassium thiocyanate, estrogens, and placebos. The effects of sympathectomy were also studied.

Results. We are reporting the common effect of different therapy rather than the effect of any particular drug or method.

1. *Evaluation of Slight Effects on the Blood Pressure Level.* Home blood pressure studies are of value in studying the effect of a form

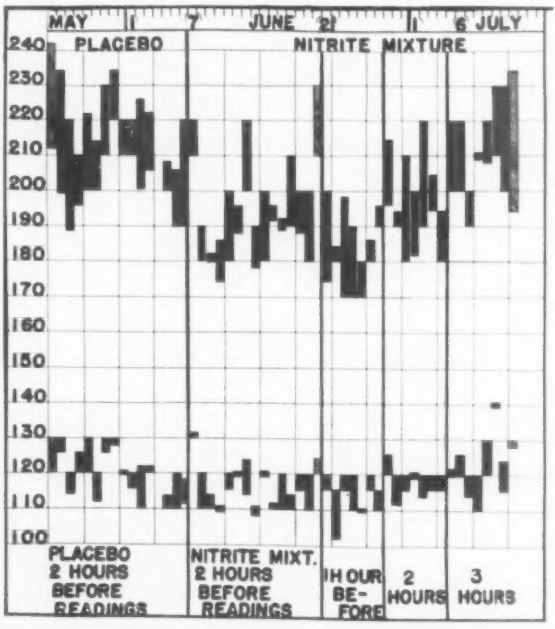

FIG. 1.—Home and clinic blood pressure readings in a patient with essential hypertension before and during treatment with a tablet containing various nitrites. Each vertical black column represents morning readings at home. Each cross-hatched column represents clinic readings. The evening home readings are not included because of lack of space. The upper black bands are systolic, and the lower ones are diastolic.

of therapy which has only small though definite effects on the blood pressure, since it permits the construction of a curve of blood pressure based on a large number of daily readings. This curve will remain at a definite level before treatment; administration of an effective drug causes the level of the curve to fall promptly and unmistakenly. It is possible, therefore, to evaluate drops in blood pressure of only 10 to 20 mm. systolic, whereas if scattered clinic readings alone are used, such decreases are not brought out. Figure 1 is a comparison of clinic and home readings before and during the use of a nitrite mixture. The effect of this drug once each morning is noted by a definite though small drop in the morning

blood pressure at home, whereas the clinic readings show no change. Since nitrites are obviously not continuous in action, their effect on the blood pressure could not be determined by clinic visits unless the drug were taken just prior to the clinic visit. In this instance, the blood pressure readings were taken at home at various intervals after taking the drug and it is possible, therefore, to note the fact that this drug had its greatest effect one hour after it was taken.

2. *Study of Small Number of Cases.* Study of home blood pressure readings has also permitted the satisfactory evaluation of drugs through the use of a small number of cases. It is apparent that results in a dozen cases studied by this method give more conclusive information than those in a much larger series studied by means of occasional clinic readings.

3. *Gives Better Understanding of the Toxic Reactions of Drugs.* Another important point clarified by the use of this method is the matter of untoward or toxic reactions to drugs. We have noted frequently that in one patient a very moderate amount of drug may give toxic reactions without any apparent drop in the clinic blood pressure, whereas in another patient the same dose and the appearance of toxic symptoms are accompanied by a drop in clinic blood pressure. It appears, therefore, that possibly in both cases the home blood pressure has dropped with the appearance of toxic symptoms, but has not been shown by the clinic readings in one case.

4. *Removes the Pressor Effect of the Physician's Presence.* The satisfactory effect of treatment is frequently masked by considering only the clinic blood pressure readings. This finding has been observed with all forms of therapy that have any effect. Figure 2 shows the blood pressure before and after sympathetic resection. Prior to operation the blood pressure in this patient was high both at home and in the clinic, although even before operation the clinic readings were higher than the home readings. Immediately following operation the home blood pressure readings dropped to normal while the clinic readings continued to be elevated and for the 2 years up to the time of writing (Nov., 1940) have continued so. It is evident, therefore, that consideration of only clinic readings in this case would have led to the conclusion that the patient still was constantly hypertensive, although there also had been a drop from the previous clinic level of around 250 to the present clinic level of 180 or so. In reality, however, this patient now has a normal blood pressure in the normal environment of her home. Similarly, in Figure 3, representing the effects of the administration of sulphocyanate, the blood pressure at home fell within a few days after beginning the use of this drug, but when the patient returned to the clinic no effect was noted in the clinic blood pressure (*v.*, mark x in Fig. 3). On the next visit to the clinic there was some drop in the clinic blood pressure and further drop in the home readings. Without the home readings, therefore, one would have concluded that the blood pressure in this case had possibly dropped a little

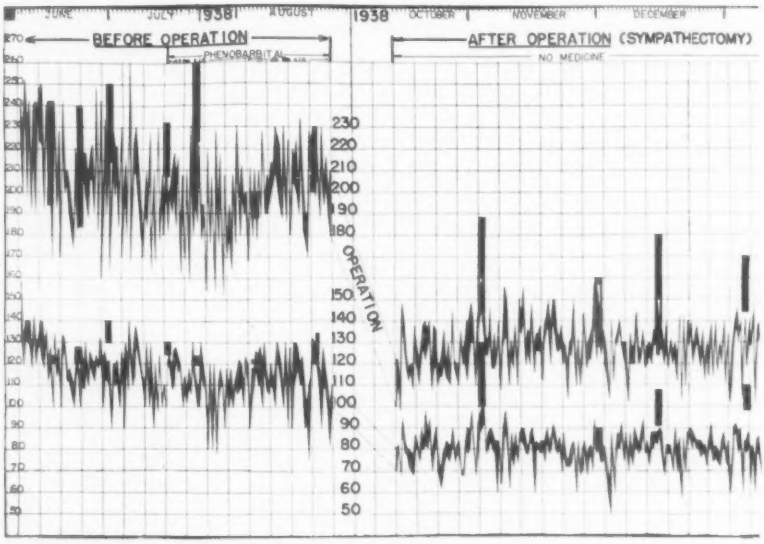

FIG. 2.—Home and clinic blood pressure readings, both before and after sympathetic resection in a patient with essential hypertension. The black wavy curves are the daily home readings: the upper black curve the systolic and the lower black curve the diastolic. The vertical broad black bands are the clinic readings.

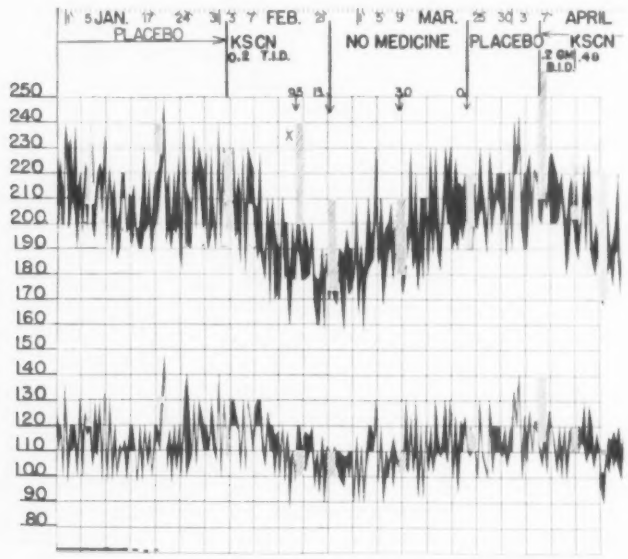

FIG. 3.—Home and clinic blood pressure curves of a patient with essential hypertension before, during and after treatment with potassium sulphocyanate. Explanation as in Figure 2. The numbers just above each arrow are the blood concentration of the potassium sulphocyanate in mg. per 100 cc. Each cross-hatched column represents clinic readings.

with the drug. However, from study of the home readings in this particular example it is clear (1) there is drop in blood pressure as a result of treatment; and (2) there is a steady rise in blood pressure following the cessation of the drug. Similar conclusions can be made from Figure 1 representing the effects of nitrites.

The difference between home and clinic blood pressure readings is due, we believe, to the fact that the doctor is a form of standard pressor stimulus similar to breath-holding[1b] or cold.[2] The operation of this stimulus overcomes the hypotensive effect of drugs or operation. On removal of this stimulus and the determination of the blood pressure at home by a member of the household or the patient himself, the hypotensive effect of therapy becomes evident. In several instances where much lower readings at home were reported, we visited the patients at home and watched while the readings were taken. In the doctor's presence these home readings were as high as those found in the clinic. Also, in all patients after we had finished taking the clinic readings, we checked their blood pressure with a double stethoscope while they themselves took the readings in the clinic, and these readings usually were the highest readings found. It may be argued that this pressor effect of the physician's presence should not be considered active in cases who have been seen month after month for years, because such patients have become accustomed to the physician. It is our experience that a patient with essential hypertension can no more become non-reactive to the physician by repeated visits than he can become non-reactive to the pressor test of cold or breath-holding. Figure 2 is an example of the failure of the development of immunity on the part of the patient to the physician's presence despite 30 visits to the doctor in 2 years.

Summary and Conclusions. The study of home blood pressure levels furnishes a valuable means for judging the effect of treatment, because of the larger number of blood pressure readings obtained at home and the absence of the pressor effect of the physician's presence. It is, apparently, not possible for the patient to develop an immunity to the pressor effect of the physician's presence on his blood pressure. The findings of this study indicate that many drugs that in the past have been regarded as without effect must be re-studied since some of them may have hypotensive effects on the home blood pressure and no discernible effect on the clinic readings. Since the patient is living the greater part of his life in an environment similar to his home, it is reasonable to accept that the home readings are a more important indication of the patient's blood pressure than the clinic readings.

We wish to thank the Baumanometer Company for the loan of mercury blood pressure machines.

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AZOTEMIA DUE TO INGESTION OF BLOOD PROTEINS.

BLOOD UREA INCREASE RELATED TO INGESTION OF WHOLE BLOOD, RED CELLS, PLASMA, AND OTHER PROTEINS.

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THE increase in blood urea nitrogen which occurs following hemorrhage into the upper gastro-intestinal tract has been the cause of much speculation among clinicians. Numerous observations on clinical cases have excluded shock, dehydration, and starvation as possible underlying factors and renal clearance studies in uncomplicated cases have failed to demonstrate any accompanying disturbance in kidney function.[1,3,4,8]

The introduction of citrated blood into the stomach, jejunum and upper ileum in humans[8] has indicated that the presence of blood in the upper gastro-intestinal tract is responsible for the observed rise in urea nitrogen. However, in such studies, all possible variable factors are controlled with difficulty.

Kaump and Parsons[6] have recently published a series of experiments in which, using dogs, they were able to demonstrate a preliminary rise in urea nitrogen directly dependent on feeding whole blood and a secondary, slight, delayed rise wholly dependent on bleeding. These authors also present a comprehensive review of the recent literature pertaining to extrarenal azotemia.

The present study is concerned with the increase in blood urea nitrogen in normal dogs, receiving standard, adequate diets, following the additional feeding of whole blood, red blood cells, plasma, casein, and lean meat. The accumulated data indicate that an elevation of blood urea nitrogen occurs after feeding each of the above mentioned substances and that the increase is directly dependent on the amount of protein in the material fed, irrespective of its form. This indicates that the globin of the hemoglobin, which accounts for approximately 70% of the protein in whole blood, is readily digested.

Therefore, one may conclude that the elevation in blood urea nitrogen which follows gastro-intestinal hemorrhage is due primarily to absorption of the digestive products of the protein of the blood.

Methods. Normal mongrel dogs, vaccinated against distemper, were used. All the animals were well nourished and received standard diets adequate, in protein and caloric content, to maintain nitrogen equilibrium and body weight. The diets were given at a definite time except on the

days of additional feeding, when they were offered following collection of the 12-hour blood sample.

All fluid materials were fed by stomach tube and the solids fed were consumed within a period of a few minutes.

Blood to be fed was obtained from normal donor dogs using as anticoagulant 1 cc. of saturated sodium citrate for each 100 cc. Red cell suspensions and plasma were obtained by centrifugation of whole blood. The plasma was pipetted off and the cells were resuspended in saline. The volume was accurately measured in each instance and aliquot portions were taken for protein determination. This was done by the macro-Kjeldahl method. The protein content of lean ground round steak was taken as approximately 22.6%.[2] Purified casein containing 85% protein as determined previously in this laboratory was used.

Blood samples for urea nitrogen and non-protein nitrogen determinations were obtained by jugular puncture, 0.1 cc. of saturated sodium citrate being used as anticoagulant for each 10 cc. of blood.

One blood sample was taken immediately before the additional protein feeding and subsequent samples approximately 3, 7, 12 and 24 hours after the feeding. In certain instances when the urea nitrogen concentration was still considerably elevated after 24 hours, an additional sample was taken 6 hours later.

All urea nitrogen determinations were carried out by the aëration method of Van Slyke and Cullen.[9] Non-protein nitrogen was determined by a modification of the micro-Kjeldahl method of Goebel, as described by Peters and Van Slyke,[7] after precipitation of the protein with 5% trichloracetic acid.

Experimental Observations. The clinical condition of all animals remained essentially normal throughout the experiments. In no instance was the appetite impaired and a slight gain in weight was usually noted. Intubation of the stomach was well tolerated. Vomiting occurred occasionally, however, following the feeding of plasma in excess of 400 to 500 cc. or large quantities of packed red blood cells and such experiments were immediately discontinued.

Tarry stools were usually noted during the 24 hours following the ingestion of whole blood or resuspended red cells. Slight diarrhea accompanied the tarry stools in a few instances.

Chart 1 shows the increases in blood urea nitrogen concentration following the ingestion of varying amounts of different materials, plotted against the hours of the experiment, in one representative series. It will be noted that the form of the curves is roughly similar in most experiments and that the time required to reach the peak is approximately proportional to the magnitude of the increase. This time interval varies from 4½ to 10 hours. In every instance the urea nitrogen concentration returns to the basal level within 30 hours and in the majority of cases it is normal in 24 hours or less. Increases in non-protein nitrogen parallel those of urea nitrogen in every respect and may be accounted for almost entirely by the rises in urea nitrogen.

Table 1 lists the outstanding features of each experiment. Column 3 indicates the type and amount of material fed, while the protein content of each feeding is tabulated in Column 4. The maximum increases in urea nitrogen and non-protein nitrogen con-

centration listed in Columns 6 and 7 were derived from the type of curves illustrated in Chart 1. In the majority of cases the figure corresponds with an actual determination; however, others were obtained by interpolation when the experimental points were obviously not at the peak of the curve. Comparison of Columns 4 and 6 reveals that the maximum increase in urea nitrogen concentration (Column 6) varies in the same direction with increases or decreases in the total amount of additional protein ingested.

TABLE 1.—BLOOD UREA NITROGEN INCREASED BY FEEDING VARIOUS PROTEINS.

Dog No.	Weight, kilos.	Additional feeding, amount and type.	Protein content of feeding, gm.	Urea nitrogen concentration, mg. per 100 cc.		N.P.N. conc. max. increase above control, mg. per 100 cc.
				Control level.	Max. increase above control.	
38–189	13.8	300 cc. whole blood	63.0*	10.60	35.90	45.0
		137 cc. packed R.B.C.	40.0*	10.90	26.10	29.0
		160 cc. plasma	10.4*	10.80	7.62	
38–23	19.6	300 cc. whole blood	63.0*	7.11	17.00	20.4
		150 cc. whole blood	31.5*	5.77	7.00	7.4
		180 cc. whole blood	36.7	8.60	8.00	10.0
		310 cc. whole blood	72.0	9.12	13.88	16.3
		500 cc. whole blood	106.0	8.95	22.30	25.0
		126 cc. packed R.B.C.	33.3	12.70	7.50	10.5
		310 cc. packed R.B.C.	86.5	5.24	17.50	23.5
		395 cc. plasma	24.2	5.91	6.57	
		500 cc. plasma	34.6	6.65	6.20	10.4
		48 gm. casein	41.0	5.72	11.20	16.0
		260 gm. lean round steak	57.0	10.70	11.42	13.2
38–11	15.6	100 cc. whole blood	22.4	12.20	6.80	7.8
		175 cc. whole blood	36.6	11.62	14.00	22.5
		305 cc. whole blood	66.7	10.69	20.00	20.0
		60 cc. packed R.B.C.	24.4	11.50	10.65	10.9
		75 cc. packed R.B.C.	31.1	8.42	8.00	
		130 cc. packed R.B.C.	53.2	12.88	19.14	22.2
		275 cc. plasma	15.7	11.04	2.00	2.0
		440 cc. plasma	26.6	8.40	7.00	7.4
		440 cc. plasma	24.2	10.23	7.88	
		50 gm. casein	42.5	10.40	13.20	13.8
		200 gm. lean round steak	42.0	14.70	12.00	13.1

Figures in Column 4 marked * were estimated, not actually determined.

In Chart 2 the protein fed in each experiment is plotted against the corresponding maximum increase in urea nitrogen concentration. It is apparent that the maximum rise in urea nitrogen concentration bears a direct relationship to the protein content of the material ingested, irrespective of its form. In view of the generally similar shape of the curves representing increases in urea nitrogen concentration (Chart 1), the value for each maximum increase will be approximately proportional to the total increase in urea nitrogen occurring after each additional feeding. These values of course give no indication of the actual magnitude of the total increase in urea.

Discussion. It has been demonstrated by previous investigators that azotemia results directly from the presence of blood in the upper portions of the gastro-intestinal tract. In the present experiments all complicating factors are absent and the data show clearly that the effects of such blood on the urea nitrogen concentration can be duplicated by either the red cell or plasma elements of the

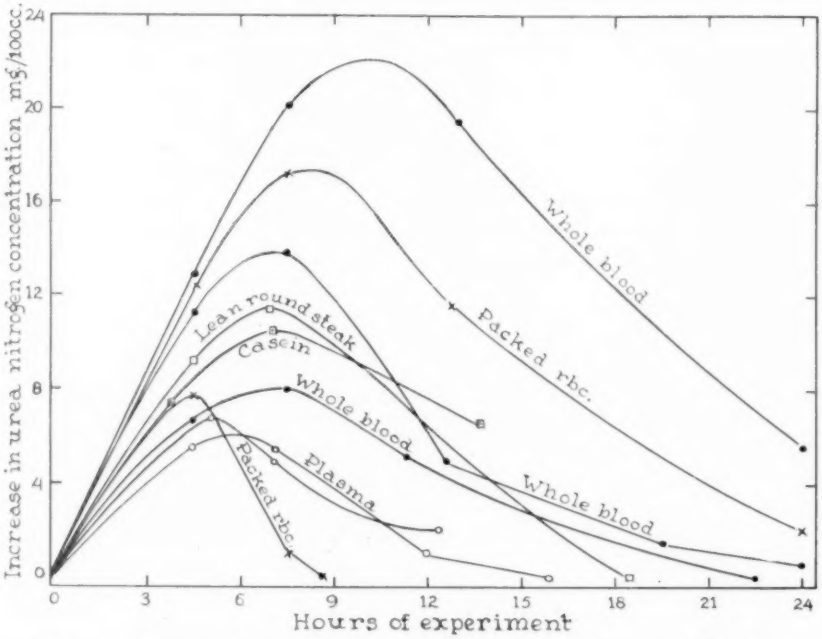

CHART 1.—Increases in urea nitrogen concentration above the control level, at varying time intervals after the ingestion of different materials.

blood, by a simple protein such as casein, or by lean meat rapidly consumed. In each case the maximum increase in urea nitrogen concentration is related directly to the protein content of the material ingested.

These findings also exclude the possibility of any toxic effect related to the absorption of breakdown products of blood as a cause of the rise in urea.

It has been assumed that hemoglobin is not digested to any great extent in the gastro-intestinal tract and this assumption has been supported by the occurrence of tarry stools following gastro-intestinal hemorrhage. It is clear from these experiments that globin, comprising 95% of hemoglobin, is as readily digested as any of the other proteins given. In certain experiments measurements were made of the excess nitrogen excreted by the kidneys during the periods of azotemia. The findings are not sufficiently complete to be included in detail, but it is interesting to note that

the most marked increases in urinary nitrogen were encountered during those experiments when the protein ingested was all in the form of *hemoglobin*. Since at times as much as 75% of the protein fed was accounted for by excess urinary nitrogen, *globin* is obviously

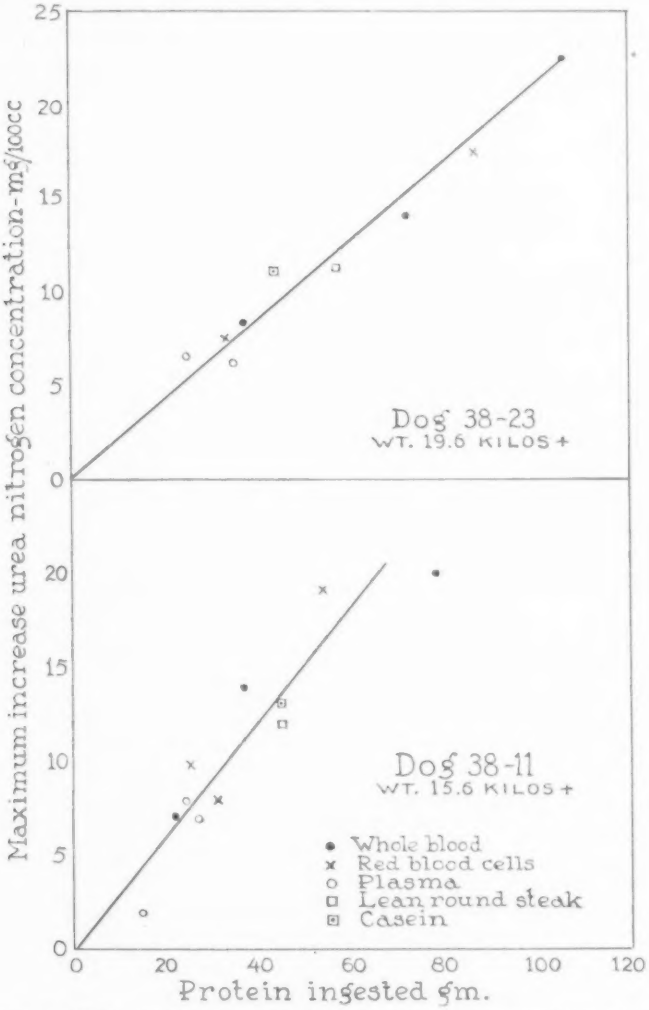

CHART 2.—The maximum increase in urea nitrogen concentration, above the control level, plotted against the protein content of the corresponding additional feeding, in two series of experiments.

digested and absorbed, though not utilized to any great extent. As a result of this, the tarry stools which follow gastro-intestinal hemorrhage probably contain largely the pigment portions of the blood. Non-utilization of the digestive products of hemoglobin have been observed previously in this laboratory. Hemoglobin

given by vein is utilized practically 100% to form new red cells by anemic dogs, as contrasted with a 10% recovery when similar amounts are fed.[10]

It has been suggested that the elevation of blood urea nitrogen may be used as a means of determining the continuance or recurrence of intestinal hemorrhage.[5] The value of this procedure is doubtful since in massive hemorrhage other signs and symptoms are more obvious and important and the slight rises accompanying small hemorrhages may be readily overlooked. Food within the intestinal tract may also confuse the picture and nullify the significance of any elevation in blood urea nitrogen.

Conclusions. The concentration of urea nitrogen in the blood increases following the ingestion of whole blood and the magnitude of the increase is proportional to the quantity of blood given.

Comparable amounts of protein fed in the form of red cells, plasma, casein, or lean meat also cause similar increases in blood urea nitrogen.

It is apparent that the elevation of blood urea nitrogen is related to the digestion of these protein materials and absorption of the digestive products from the intestinal tract. The globin in hemoglobin is obviously digested as readily as any other protein.

Shock, dehydration, starvation, or impaired renal function are not necessary factors in the production of the azotemia observed following hemorrhage into the upper gastro-intestinal tract.

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THE ELECTROCARDIOGRAM DURING ELECTRIC SHOCK TREATMENT OF MENTAL DISORDERS.

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The convulsive treatment for schizophrenia and other psychoses, first insulin and later metrazol, has been used with favorable results

since its popularization a few years ago. Most recently, convulsions have been produced by means of electric shock. Due to its simplicity, favorable reaction of the patient and the good results obtained, this procedure has gained considerable popularity. Although there is considerable information in the literature concerning the effect of severe grades of electric shock upon the organism in general and upon the heart in particular, we have been able to find no reference concerning cardiac and particularly electrocardiographic studies in the less severe type of shock treatment. In view of the possible effects of this procedure on the heart, it was considered of interest to study the cardiovascular response and particularly the electrocardiographic alterations incident to this type of therapy.

Procedure and Apparatus for Inducing Electric Shock. In 1938, Cerletti and Bini,[5] encouraged by preliminary experimental studies in dogs, announced their use of electrically induced convulsions for the treatment of schizophrenia. Several investigators[2–4,6,7,13,16,17a,b] corroborated their findings and agreed that the method has definite advantages over other forms of convulsive therapy.

The apparatus devised by Cerletti and Bini[5] and modified by Fleming, Galla and Walters,[6] utilizes alternating current of 110 volts. Step-down and step-up transformers are so arranged that the voltage can be regulated from 0 to 220 volts. Metal salt-soaked electrodes are placed over the frontal poles of the head; utilizing a low tension circuit (4.5 volts), the voltage is adjusted so that approximately 1 milliampere of current is delivered. The voltage is then read on a voltmeter and from Ohm's law $\left(\text{amperes} = \frac{\text{volts}}{\text{ohms}}\right)$ the resistance is computed. This ranges between 450 and 1200 ohms. Exact calculation of the resistance is superfluous, as Cerletti emphasizes that Ohm's law does not apply to living tissues over a wide range of strong current strengths. The apparatus used in these experiments was therefore further modified so that the head resistance could be read directly on an ohmmeter with the voltage maintained at an empirical level (usually 80 volts). The high tension circuit is then turned on and an automatic timer which regulates the duration of flow of current from 0.1 to 1.0 is pressed. The average convulsive threshold ranges between 80 to 150 volts, 200 to 300 milliamperes and 0.25 to 0.50 second.

By this method of application, the electric shock passes through the animal body as though it were passing through a structureless gel, always choosing the shortest path from contact to contact without deflection by anatomic landmarks.[18]

The patient undergoing treatment may experience one of three reactions: 1. A momentary loss of consciousness preceded by a sudden start but without any muscular contractions. Sparks or

flashes of light may appear before the eyes, but the subject otherwise cannot recall what has happened to him. 2. A subconvulsive reaction. Following the start, facial twitchings appear and occasionally coarse tremors of the arms and legs. Unconsciousness lasts from 5 to 10 seconds. Mild cyanosis, sucking movements, confusion and verbigeration, singing or laughing may result. Amnesia for

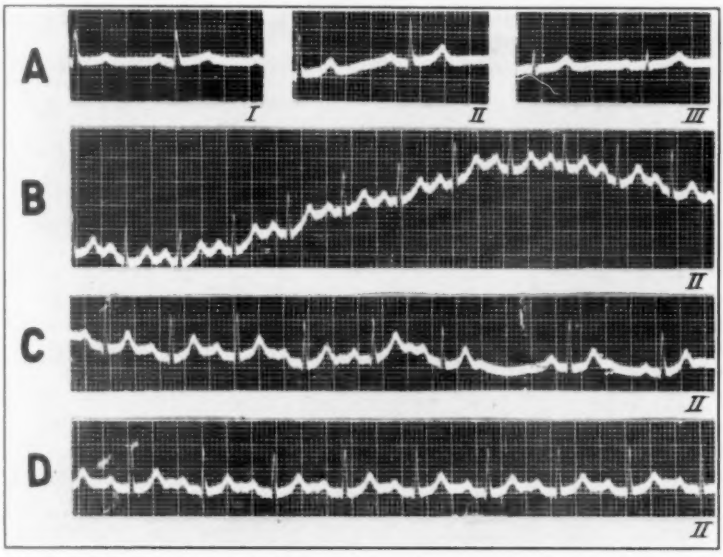

FIG. 1.—Represents typical changes observed. *A*, Leads I, II and III control, before electric shock. *B*, one minute after electric shock. The previous rate of 75 was increased to 145 per minute. *C*, Three and a half minutes after electric shock. Rate has slowed to 115 per minute. Occasional cycles of sinoauricular heart block. *D*, Four and a quarter minutes after electric shock. Normal rhythm, rate 107 per minute.

the episode is complete. 3. A convulsive reaction. There is a sudden severe generalized tonic spasm followed by facial twitchings, upward deviation of the eyes, pupillary dilatation, flexor tonus of the extremities, gradually giving way to clonic movements, apnea, cyanosis, salivation and finally hyperpnea. A cry usually does not occur. Amnesia is complete from the time of placing the electrodes to shortly after regaining consciousness.

Tonic spasm and a tendency to dislocation of the jaws is prevented by a suitable mouth gag and counter-pressure. Gentle restriction by holding the arms, hips and legs and maintenance of hyperextension of the vertebral column on a rigid wooden table may prevent fractures and dislocations.

The seizure lasts 30 to 45 seconds. A period of unconsciousness lasting 5 to 10 minutes follows the seizure and the patient passes through a short period of confusion before awakening. Restlessness,

nausea or vomiting after treatment are minimal in comparison with metrazol shock treatment. Sleep lasting 1 to 3 hours usually follows. Lassitude and moderately severe headache are frequent complaints, but these gradually give way to a feeling of well-being. Fear of treatment is rarely encountered.

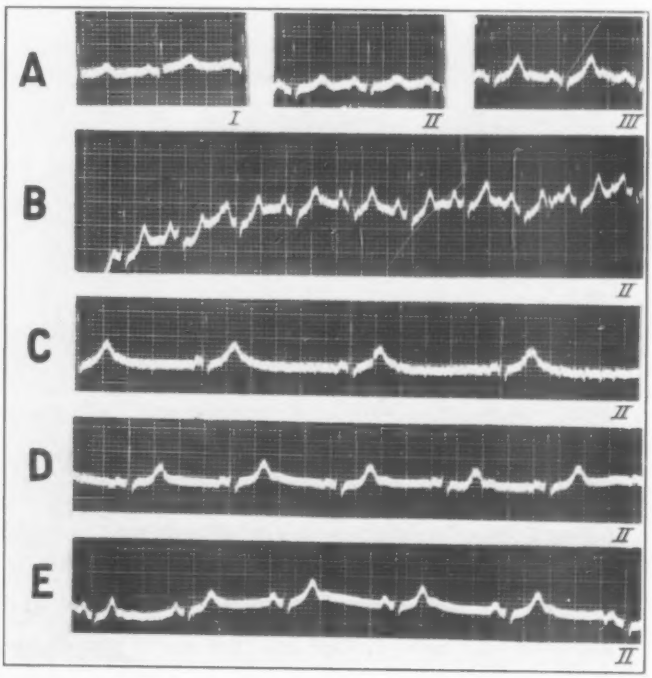

FIG. 2.—*A*, Leads I, II and III before convulsions. *B*, one minute after electric shock. Note increase in rate to 140 per minute. *C*, two and a half minutes after electric shock. Regular rhythm, rate 50 per minute. Short *PR* intervals, measuring 0.08 second, probably resulting from shift in pacemaker to lower portion of sinus node or to upper portion of *A–V* node. *D*, five minutes after electric shock: rate 72 per minute. *P* waves are still inverted but *PR* intervals now measure 0.12 second. The inverted *P* waves probably suggest that the pacemaker is situated in a different portion of the sinus node as compared to the normal. *E*, six minutes after electric shock; normal sinus rhythm, rate 68 per minute, *P* waves and *PR* intervals are now normal.

Choice of Patients. In our study, each patient was examined from the cardiovascular standpoint before therapy was instituted. This examination included orthodiagraphic and electrocardiographic studies. Only those patients in whom there was no clinical evidence of cardiac involvement were chosen. However, the presence of arteriosclerotic change in the older age groups could not be ruled out. Before application of the current, a control electrocardiogram (Leads I, II and III) was taken. During the convulsive seizure, where feasible, continual electrocardiographic tracings (Lead II)

were taken and at frequent intervals thereafter until the tracing returned to normal. This usually required 7 to 15 minutes from the onset of the convulsive seizure. In 3 cases in which electrocardiographic studies were made, 1/30 gr. atropine was administered subcutaneously before the shock. In 3 cases, curare was administered intravenously before the shock, 1 cc. per 15 pounds of body weight, for the purpose of diminishing the somatic effects of the convulsive seizure.

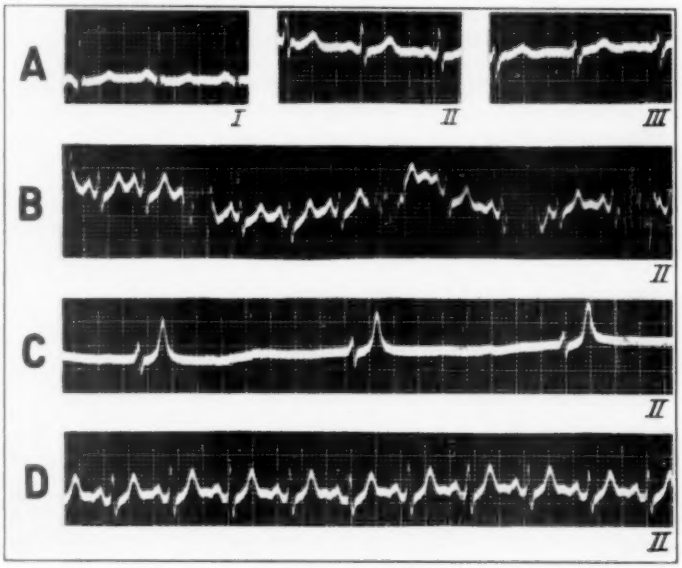

FIG. 3.—*A*, control, before electric shock. *B*, one minute after electric shock. Tachycardia, rate 150 per minute. *C*, two minutes after electric shock. Extremely slow ventricular rate, 35 per minute and absence of *P* waves. This is due either to long sinus pauses or an *A–V* nodal rhythm. *D*, five minutes after electric shock. Normal sinus rhythm, rate 125 per minute.

This report is based on 100 electrocardiographic studies during electric shock treatments in 50 patients, 65 of these studies were made on patients having major seizures and 35 on patients with minor seizures. The following were the age groups of our patients:

TABLE 1.—AGE GROUPS.

Age.	Cases.	Age.	Cases.
10–19	2	50–59	9
20–29	10	60–69	1
30–39	15		—
40–49	13	Total	50

Fourteen of our patients were male and 36 female. The mental disorders treated were: manic-depressive psychosis, 28; schizophrenia, 17; and psychoneurosis, 5.

Findings. Table 2 is a summary of the electrocardiographic changes which were obtained. In 12 studies, no electrocardiographic effects were detected. All 12 patients who showed no electrocardiographic effects had developed only minor seizures. Eighteen of the 22 patients who showed no increase in rate, had developed only minor seizures. In the group having major seizures, there was no definite correlation between the severity and length of the convulsive seizure and the grade of electrocardiographic effect. Likewise, there was no apparent relationship between the electrical dosage utilized in producing a convulsion and the severity of the electrocardiographic effects.

TABLE 2.—SUMMARY OF ELECTROCARDIOGRAPHIC EFFECTS.

	No. of observations.
Minor disturbances in rhythm:	
Sinus arrhythmia	26
Sinus bradycardia	7
Sino-auricular block	4
A–V nodal rhythm	2
Shifting pacemaker	3
Auricular extrasystoles	1
Total	43
T wave and ST changes in Lead II:	
T wave inverted	2
T wave flat	7
T wave increased height	6
ST segment depressed	3
Total	18
Changes in rate:	
Increased in rate to 120 to 150 per minute	66
Decrease in rate (occurring alone) to 55 to 60 per minute	18
Total	84

Atropine and Curare Studies. In 3 cases atropine sulphate, 1/30 gr., was administered subcutaneously 30 minutes before the electric shock, to patients who had previously developed rather marked electrocardiographic changes following their seizures. One patient who had previously developed a sinus bradycardia, sinus arrhythmia and slow nodal rhythm, following atropine, merely developed a minor reduction in cardiac rate from 150 per minute to 140 per minute. A similar type of change was recorded in the 2 other patients who received atropine. The effects in these patients during previous treatment had consisted of sinus arrhythmia and a very slow sinus rate.

Curare was administered to patients prior to convulsive therapy in order to minimize the systemic complications occurring during a convulsive seizure, particularly fractures of the vertebræ. Curare does this by partial paralysis of the nerve endings in the skeletal muscles. Following its administration, however, impairment of the activity of the accessory muscles of respiration may often occur and may at times be conducive to long periods of apnea. Three

patients received curare (1 cc. per 15 pounds of body weight administered intravenously at a very slow rate) before the administration of the electric shock. In 2 of the patients (ages 15 and 30) the electrocardiographic changes following the convulsive seizures were of the same order as those recorded when curare was not administered; namely, a tachycardia followed by a sinus arrhythmia. The third case, a patient of 54 years, developed a more severe reaction, which will be discussed below.

Untoward Effects. Untoward effects during electric shock therapy were observed under unusual circumstances in 2 patients of 54 and 47 years, respectively. These are discussed below:

Case Abstracts. CASE 1.—T.M., a colored male of 54, was admitted to the psychopathic ward with a diagnosis of involutional psychosis. His medical history, including the cardiovascular history, was negative. Physical examination revealed no abnormalities. Serology was negative, as were other laboratory findings. Blood pressure was 148/74. The control electrocardiogram, taken 2 days before the treatment, was within normal limits, showing only very slight flattening of T_1 and T_2. The orthodiagram was normal. The electrocardiographic changes following curare and electric shock are illustrated in Figure 4. This shows the development of an idioventricular rhythm with widened ventricular complexes and ventricular extrasystoles; 15 minutes elapsed before the electrocardiogram returned to normal. These effects suggest a rather serious type of myocardial disturbance. Electric shock given to the same patient without curare at several later dates did not produce the severe effects seen when the curare had been given.

The convulsive seizure following shock is often followed by a short period of apnea. Curare by its depressing effect on the accessory muscles of respiration could still further prolong this apneic period with resulting impairment in function at a time when the heart work is already considerably increased. Such effects would be obviously more serious in older patients with arteriosclerotic change in the heart muscle.

CASE 2.—F.D., a white female of 47, was admitted July 22, 1940, to the psychopathic ward with a diagnosis of involutional melancholia with suicidal tendencies. She was severely undernourished and on admission weighed 87 pounds, a loss of 100 pounds having occurred in the previous year. No symptoms were referable to the cardiovascular system. Examination revealed no evidence of abnormalities in the chest or abdomen. Blood pressure was 140/100. Laboratory findings, including urine, blood count and Wassermann test, were negative. Blood chemistry was normal. The basal metabolic rate was +3. Roentgen ray of the skull was negative. On September 7, electric shock treatment was given, resulting in a minor seizure. About an hour later, this patient developed a series of severe major convulsive seizures during which she became cyanotic, and artificial respiration was required. The administration of ether anesthesia and intravenous sodium barbital was required for their abolition. An electrocardiogram taken after the series of seizures ceased, showed little change from the control. Subsequent tracings, however, showed considerable change as shown in Figure 5. These consisted of the development of inverted T waves in Leads I, II and CF_4, which after 6 weeks had not returned to normal. At no time did this patient complain of precordial pain or manifest

any signs of marked cardiac derangement, except for a minor drop in blood pressure to 120/90 and leukocytosis of 14,000. There was no increase in temperature at any time.

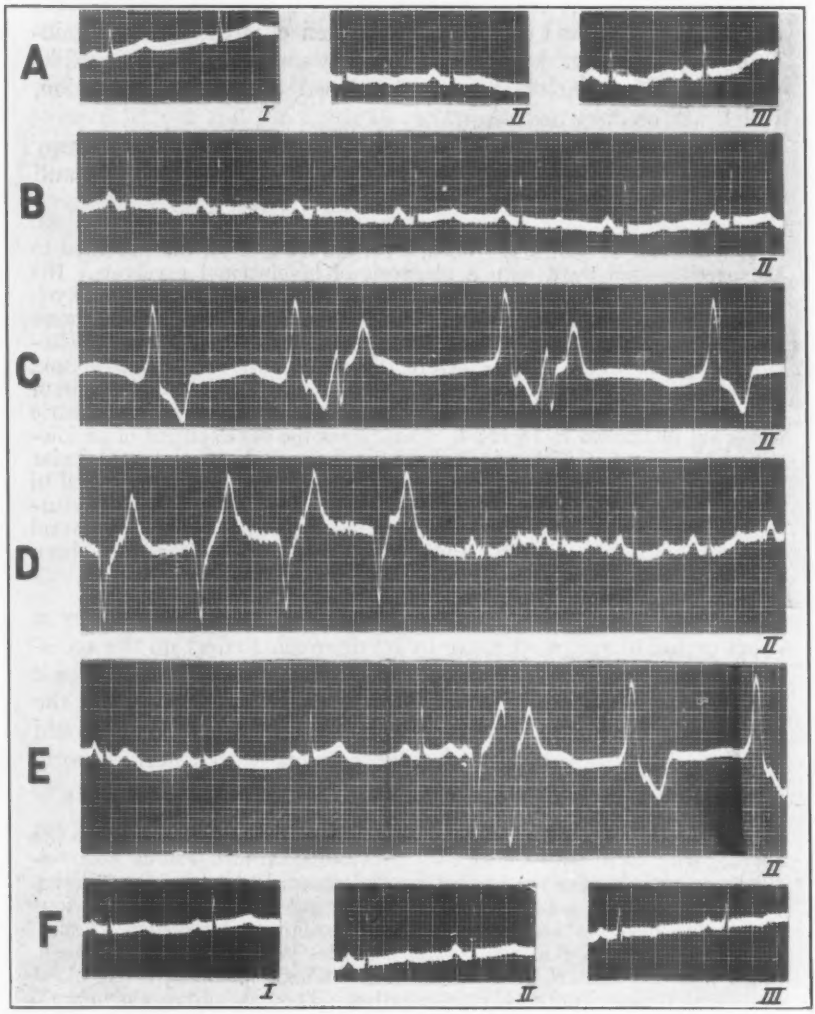

FIG. 4.—*A*, control, before electric shock. *B*, Lead II, 1 minute after curare 8.7 cc. was administered. Normal sinus rhythm is present with somewhat diminished amplitude of *T* waves. *C*, one minute after electric shock. Respirations shallow and slow. Idioventricular rhythm with aberrant widened ventricular complexes accompanied by frequent ventricular extrasystoles. *D*, four minutes after. Artificial respiration had been instituted. Aberrant ventricular complexes. Rate: 78 per minute, later merging into normal complexes with sinus rhythm. *E*, ten minutes after. Respirations still shallow and slow. Initial cycles of normal rhythm are followed by two ectopic ventricular beats occurring in succession, initiating a slow ectopic ventricular rhythm. Normal sinus rhythm has returned 15 minutes after electric shock had been given. *F*, normal rhythm, Leads I, II and III, as recorded 2 days later.

Delayed convulsive seizures such as were exhibited by this patient have been observed in occasional cases after metrazol and are probably related to the initial convulsion. The presence of the profound change in the electrocardiogram in this patient (Fig. 5) indicates that a severe derangement occurred in the myocardium. We are uncertain as to the condition responsible for these alterations. From postmortem examination of other cases dying in convulsive seizures, however, we know that it is possible that a hemorrhage into the ventricular musculature may have occurred. It is interesting that similar electrocardiographic changes have been reported by Levine, Piltz and Reznikoff[14] following metrazol convulsions in 2 cases.

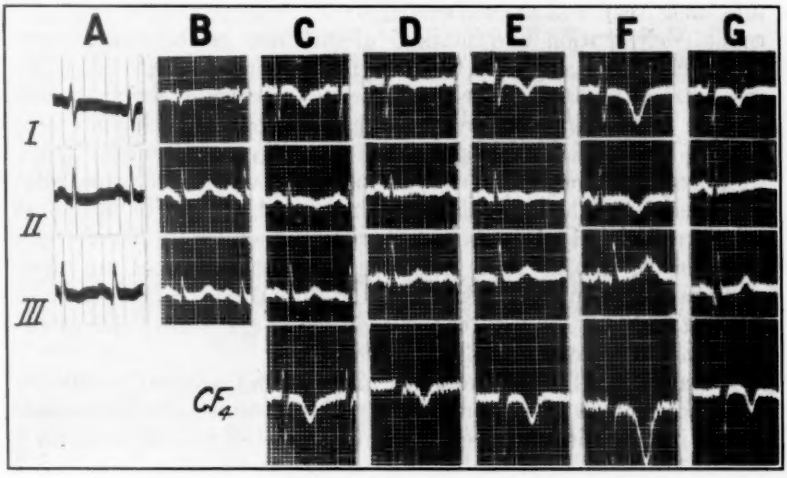

FIG. 5.—*A*, F.D., Case 2. September 5, 1940: Control. Note flattened *T* waves, depressed *ST* intervals in Leads II and III. *B*, September 7: one hour after series of convulsions. *C*, September 9: inversion of *T* waves in Leads I and II and CF_4 with tendency to right axis deviation. *D*, September 11: less marked inverted T_1, upright T_2 and T_3. *E*, September 17: resembles *C*. *F*, September 26: changes are more marked, inversion of T_1 and T_2 is rather deep, inversion of *T* and CF_4 is of considerable amplitude. *G*, October 24: T_1 still inverted, T_2 flat, T_3 upright, *T* of CF_4 still inverted.

Discussion. Certain electrocardiographic changes would not be unexpected in any type of convulsion. In that produced by electric shock, there are several factors that may influence the heart and the electrocardiogram: *a*, the strain upon the heart resulting from the mechanical effect of the convulsive seizure; *b*, certain reflex and indirect effects on the sympathetic and parasympathetic nervous systems.

As a result of the increased blood pressure which occurs during convulsive seizures, a great strain is suddenly placed upon the cardiovascular system. While in young individuals free from disease this usually is of little moment, the possible effect of such strain on the heart and vascular system must be taken into consider-

ation in older patients in whom arteriosclerotic changes are present. As a result of the sympathetic effect,* there is an increase in the cardiac rate, which usually ranges from 120 to 150 per minute. This increase is of short duration, lasting from 1 to 2 minutes. This increase in rate is usually followed by vagal effects with resultant slowing of the heart rate, which then drops to 40 to 60 per minute. Such effects are to be considered of a minor character and as the indirect result of vagal stimulation. They do not indicate any direct effect upon the muscle itself. Vagal effects were abolished in all 3 instances in which atropine was administered.

Comparison of the Effects of Insulin Shock, Metrazol and Electrical Shock on the Electrocardiogram. Convulsions occurring during insulin shock treatment are associated with a severe grade of hypoglycemia, dehydration and marked disturbance in the electrolytes. These changes occur at a time when the work of the heart is increased. As a result, severe strain upon the cardiovascular system is often induced and noteworthy electrocardiographic changes were obtained in two-thirds of a series of 58 shock treatments.[1] These were frequently of an order suggesting a severe type of myocardial derangement. The convulsions produced by the injection of metrazol are associated with cardiac strain but much less in degree than that due to insulin. The electrocardiographic changes are often slight, although more marked types of alterations are occasionally encountered, *e. g.*, *T* wave changes, auricular and ventricular extrasystoles and auricular fibrillation.[10,15]

The alterations in the cardiovascular system produced by electric shock were much less severe than those in insulin convulsions and, except in the 2 instances cited, showed none of the more marked electrocardiographic changes observed with metrazol.

Although the number of studies performed in this series of experiments is not considerable, from the evidence so far accumulated it would appear that the convulsion produced by electric shock results in comparatively slight strain on the cardiovascular system.

Summary and Conclusions. The electrocardiographic alterations during 100 convulsive treatments produced by electric shock were recorded in 50 different patients. Of these, 65 were major and 35 were minor seizures. In this series, the electrocardiographic changes were of a minor degree in 98 shock treatments. These included minor arrhythmias, *e. g.*, sinus arrhythmia, sinus bradycardia, sino-auricular heart block in 35 instances, *A–V* nodal rhythm in 2, shifting pacemaker in 2, auricular extrasystoles in 1. Slight changes in the *T* and *ST* segment in Lead II were observed in 18 instances.

* Gellhorn,[8] Gerard,[9] Himwich,[12] Hartman[11] and others believe that the fundamental influence of convulsive shock therapy as well as hypoglycemic shock is through the production of cerebral anoxia. The deprivation of oxygen results in powerful sympathetic stimulation. The vagal effects are probably related to the period of apnea which often follows the convulsive seizure.

In only 2 instances were more serious results encountered under unusual circumstances in older patients, ages 47 and 54 respectively. The first consisted of the production of inverted *T* waves in Leads I and II following a delayed convulsive seizure and the second a serious type of arrhythmia following electric shock after curare.

We are very much indebted to Joseph Hughes, M.D., Chief of Laboratory Service of the Pennsylvania Hospital, who devised and constructed the apparatus used in this work.

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CHANGES IN THE ELECTROCARDIOGRAM AND IN THE CARDIAC RHYTHM DURING THE THERAPEUTIC USE OF POTASSIUM SALTS.

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The rôle of the potassium ion in cardiac physiology has been extensively studied since Howell[5] indicated the influence of various cations on the automatic contractions of heart muscle. Mathison[8] in 1910 first observed ventricular fibrillation during the administration of potassium salts to animals. By means of electrocardiograms Nahum and Hoff[9] concluded that ventricular fibrillation was to be attributed to production of widespread block in all parts of the heart. Winkler, Hoff and Smith[20] were of the opinion that there was some highly specific effect of potassium on the heart muscle itself, not shared by skeletal muscle generally.

Chamberlain, Scudder and Zwemer[4] showed that increase in the potassium content of the blood of cats was associated with lowering or inversion of *T* waves, auriculoventricular and intraventricular

heart block, auricular standstill or auricular fibrillation, and ventricular tachycardia or tachysystole, ventricular fibrillation and ventricular standstill. In patients with Addison's disease, Thomson[18a] found increased amplitude of *T* waves when the serum potassium was high followed in some cases by decrease in amplitude when the level fell as a consequence of treatment. Bamber[1] in 1935 described inversion of *T* waves in a patient with syphilitic heart disease who received potassium iodide. More recently, Thomson[18b] has observed changes in *T* waves, occurrence of first-degree heart block and of auriculoventricular rhythm on the administration of potassium chloride and potassium citrate to patients. In view of the trend in the therapeutic use of potassium salts these studies are especially significant. Sampson and Anderson[13] advocated large doses of potassium salts in the treatment of auricular and ventricular ectopic beats and tachycardias. Barker[2] observed the diuretic action of potassium chloride in the relief of anasarca and his observations were confirmed by Keith and Binger.[6] More recently potassium salts have been employed in the treatment of neuromuscular disease,[7,19] in allergic states,[3,12] and their use in the therapy of hypertension has its advocates.[10] Stewart, Smith and Milhorat[17] reported lengthening of the *P–R* time, prolongation of the *QRS* time and increase in the *Q–T* interval as well as change in the form of the *R–T* segments and in the amplitude and form of the *T* waves in the electrocardiogram when the potassium content of the serum was low during the paralytic phase of familial periodic paralysis. These changes were attributed to a modification of one of the fundamental properties of heart muscle, namely conduction, by the low potassium concentration. Reversal in form of the electrocardiogram to its usual configuration occurred together with disappearance of paralysis on the administration of potassium chloride by mouth and restoration of the potassium level of the blood.

Since electrocardiographic observations have given evidence of change in the behavior of heart muscle with variation in the potassium levels, we analyzed the records of patients in the clinic in whom electrocardiographic alterations had been recorded during the administration of potassium salts. We have observed 5 patients in whom abnormal electrocardiographic changes were associated with the administration of potassium salts when given in the usual therapeutic amounts. These changes were characterized not only by changes in contour of the complexes of the electrocardiogram but also the occurrence of abnormalities of rhythm. To 1 patient potassium chloride was given as a diuretic; to 3, potassium iodide was given in treatment of cardiac syphilis; and finally, to the other patient potassium iodide was given as an expectorant. No attempt was made to examine the records of all patients receiving potassium salts nor were these drugs given in an attempt to reproduce the changes encountered in course of routine therapy of patients. Ade-

quate control records were available in each of these patients. Several patients were excluded from the study because of the lack of adequate control records, or of the giving of digitalis at a time when it confused the patterns. The current use of potassium salts in therapeusis, including the widespread administration of potassium iodide to patients with syphilis, especially of the cardiovascular system, makes these observations timely.

Case Abstracts. CASE 1.—F. S., Hist. No. 228926, a male, aged 65, was admitted to hospital complaining of pain in the left chest. He contracted syphilis 22 years earlier and received 5 intravenous and intramuscular injections at weekly intervals. In March, 1939, when he fractured several ribs, a Roentgen ray revealed aneurysm of the aorta and the Wassermann reaction of the blood was 4+.

On admission to hospital, the other significant findings were as follows: The blood pressure of the right arm was 130/80 mm. Hg and of the left 100/84 mm. Hg; there were no signs of aortic insufficiency nor of congestive heart failure; there was no evidence of neurologic involvement.

Course. An electrocardiogram was taken on admission. Tachycardia and low-grade fever resulted when the patient was given saturated solution of potassium iodide, 2 cc. (2 gm. KI), three times a day. A second electrocardiogram was taken at the end of 1 month because of persistent tachycardia despite rest in bed. On discharge, the patient was followed in the Out-Patient Department and was given bismuth and neoarsphenamine. He tolerated therapy well and remained free of symptoms. He also received potassium iodide but the dosage was not recorded accurately nor was there a record of the pulse rate. In the analysis of his data, it appeared that tachycardia was associated with the use of potassium iodide and it was decided to test this opinion by repetition of the observations. Consequently, the use of potassium iodide was discontinued and at the end of 3 weeks an electrocardiogram was taken to serve as a control for subsequent as well as against earlier potassium effects. After he had been given 2 cc. of saturated solution of potassium iodide three times a day for 1 week, another electrocardiogram was taken. During this time, a skin rash appeared.

Electrocardiograms. On admission the electrocardiogram showed left axis deviation as the only abnormality (Fig. 1, *a*). After the patient was given potassium iodide for 1 month, the rate increased to 111 per minute (Fig. 1, *b*). The *T* waves decreased in amplitude and the left axis deviation disappeared. In the first record of a second series (Fig. 1, *c*), when potassium iodide had been withheld for 3 weeks, the heart rate decreased to 83 per minute, and the *T* waves increased to their former amplitude (Fig. 1, *a*). After the patient was given potassium iodide again for 1 week, the heart rate increased to 107 per minute. In this record (Fig. 1, *d*), the *T* waves were also of slightly lower amplitude. After the patient had not received the drug for 1 week, slowing of the heart rate to 91 per minute occurred (Fig. 1, *e*).

This patient with syphilitic aneurysm of the aorta was given two courses of potassium iodide. On each occasion increase in heart rate, decrease in the amplitude of the *T* waves and iododerma occurred only to disappear when the drug was discontinued (Table 1).

CASE 2.—J. L., Hist. No. 131140, a male, aged 64, was admitted to hospital on February 8, 1940, because of progressive shortness of breath for 1 year. The patient had been given 20 injections of salvarsan following an attack of gonorrhea at 39 years but denied any knowledge of syphilis or of positive serology. One year before admission he experienced exertional

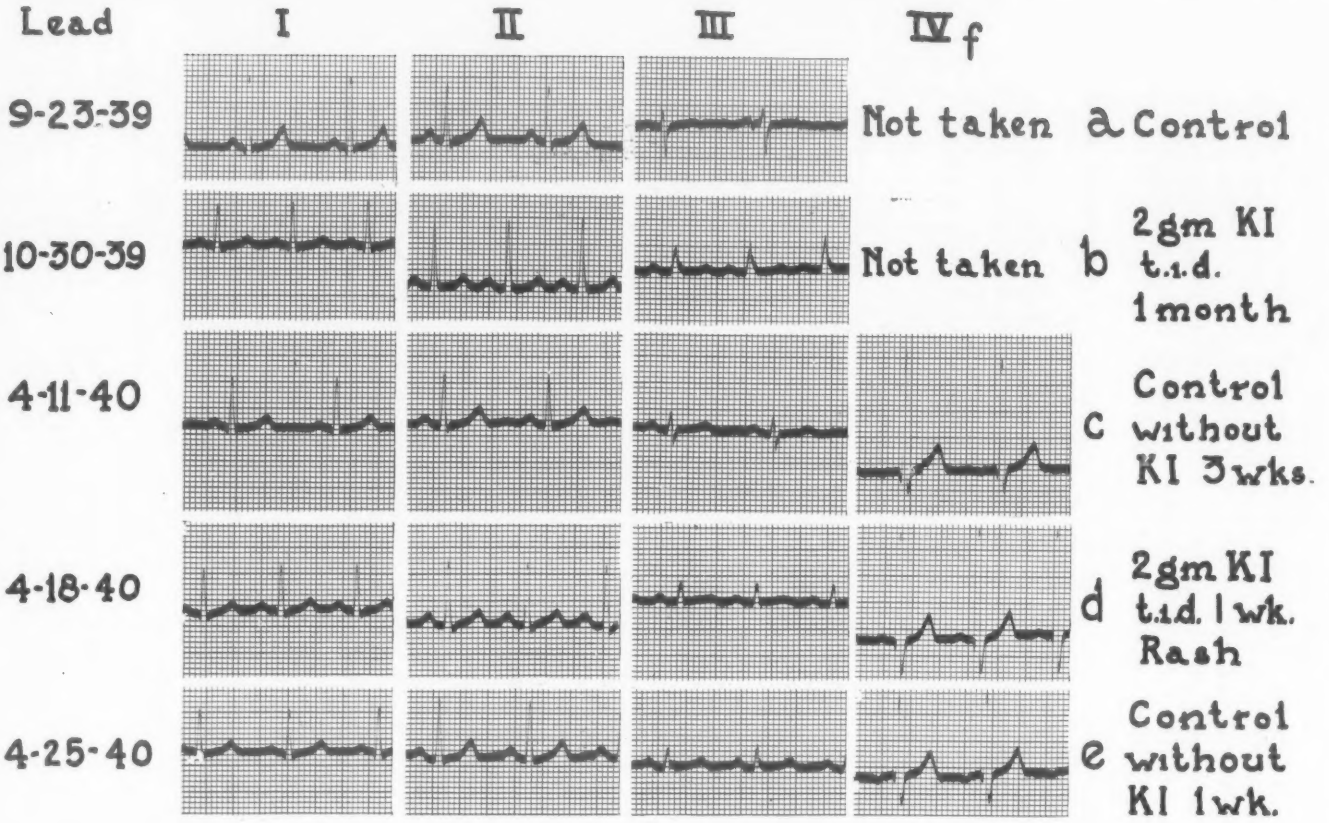

FIG. 1.—In this as well as in Figures 2, 4, 5, 6 and 7 are reproduced electrocardiograms derived from the three standard leads and Chest Lead IV f. The chest lead is the derivation recommended by the American Heart Association's Committee on Standardization of the Chest Lead.[15] The standardization in all leads was such that 1 millivolt produced 1 cm. deflection of the string. Divisions of the ordinates equal 10^{-4} volt. Divisions of the abscissæ equal 0.04 second. In this and the following figures KI = potassium iodide, KCl = potassium chloride, $BaCl_2$ = barium chloride, and $CaCl_2$ = calcium chloride. In this figure the electrocardiograms of F. S. (Case 1, Hist. No. 228926) are reproduced. For description see text.

barium chloride, and $CaCl_2$ = calcium chloride. In this figure the electrocardiograms of F. S. (Case 1, Hist. No. 225525) are reproduced. For description see text.

TABLE 1.—COMPARISON OF RESULT OF GIVING POTASSIUM SALTS TO CATS AND TO PATIENTS IN THERAPEUTIC AMOUNTS.

		Heart rate.	*T* waves.	*R–T* segments.	*A–V* conduction.	Rhythm. Auricles.	Rhythm. Ventricles.	*QRS* conduction.	Result.
Cats		Tachysystole	Lowering or inversion	IN LABORATORY ANIMALS (4). Changed in form	Block	Auricular fibrillation Auricular standstill	Vent. tachycardia Vent. tachysystole Vent. fibrillation Vent. standstill	Intraventricular heart block	Cessation of heart beat and death
Case 1 F. S.	1st administration	Tachycardia	Decrease in amplitude	IN THIS SERIES OF PATIENTS.*	..	....	....	..	Rash present. Changes disappeared with cessation of KI
	2d administration	Tachycardia	Decrease in amplitude	....	..	....	....	..	Rash present. Changes disappeared with cessation of KI
Case 2 J. L.	1st administration	Tachycardia	Decrease in amplitude	$R–T_1$ changed in form	..	....	....	..	Rash present
	2d administration	Tachycardia	Decrease in amplitude	$R–T_1$ changed in form	..	....	....	..	Form of electrocardiogram reverted to normal with cessation of KI
	3d administration	Tachycardia	Decrease in amplitude	$R–T_{1,2,4}$ depressed $R–T_2$ elevated	..	....	....	..	Rash present; Electrocardiogram resumed form before KI
Case 3 A. M.		Tachycardia	T_1 incr. ampl. T_2 more neg.	$R–T_2$ more diphasic $R–T_3$ more depressed	Prolonged *P–R* time	....	....	..	Form of electrocardiogram reverted to normal when KI was discont.
Case 4 J. G.		Tachycardia	$T_{1,2}$ more negative	$R–T_{1,2,3}$ changed form	Prolonged *P–R* time	Complete *A–V* dissociation on 3 occasions	Irregular response of the ventricles; ? vent. fibrillation	..	Free of symptoms and abnormal rhythm after KI was discontinued
		Tachycardia	....	....	..	Paroxysmal supraventricular tachycardia	....	..	
Case 5 H. K.		....	....	....	..	Auricular standstill	....	Prolonged *QRS* time	Death

* The patients are arranged in the order of the severity of the toxic signs.

dyspnea, and ankle edema appeared at the end of the day. For 8 days preceding admission he suffered a respiratory infection. He was obese and had signs of pulmonary emphysema with superimposed bronchitis. The heart was enlarged to the left; there was no evidence of aortic or mitral valvular lesions. The blood pressure was 184/116 mm. Hg. The peripheral vessels were sclerotic. The signs of cardiac failure were slight edema over the sacrum and ankles, and enlargement of the liver. There were no signs of syphilis of the central nervous system.

Course. The patient was kept at rest in bed with limited fluid and low salt intake and became free of signs of failure without the use of digitalis or other diuretics. Two cubic centimeters of saturated solution of potassium iodide (2 gm. KI) was administered three times a day as an expectorant. During hospitalization signs of congestive failure and coronary pain did not occur. The patient left the hospital against advice.

Electrocardiograms. An electrocardiogram taken shortly after admission revealed left axis deviation with normal sinus rhythm as well as normal conduction times (Fig. 2, *a*). There was low amplitude of the *T* waves in all leads including the Chest Lead IV f. The patient had received 4 gm. of potassium iodide 12 hours before this record was taken. After he had received 2 gm. of potassium iodide three times a day for 4 days, the heart rate increased (Fig. 3) and he exhibited an iodide rash. In an electrocardiogram taken at this time (Fig. 2, *b*), the heart rate was 107 per minute, R–T_1 had changed markedly in form and T_1 had become diphasic and R–T_4 had changed form and T_4 had become diphasic. At this time we were not fully aware of the effects of potassium salts given in therapeutic amounts on the form of the electrocardiogram and it was the opinion that he may have sustained recent coronary occlusion or pulmonary infarction. When the drug was discontinued for 4 days, however, T_1 increased in amplitude, changed form and became upright as did T_4 and the heart rate became slow, so that the electrocardiogram assumed a normal configuration except for the presence of left axis deviation (Fig. 2, *c*). There were now no deformities to suggest coronary artery disease. This record (Fig. 2, *c*) served as a control for this patient. The patient was then given the drug, potassium iodide, 6 gm. daily, for 2 days, and T_1 decreased in amplitude, T_3 changed form and the heart rate increased again (Fig. 2, *d*).

Second Admission. The patient was readmitted to the hospital on April 2, 1940, complaining of recurrence of dyspnea, edema of the ankles and sense of weight in the abdomen. There was a small amount of fluid in the peritoneal cavity.

Course. The regimen was similar to that instituted on the first admission. On this occasion, however, because of cardiac failure, 1.8 gm. of digitalis was given in 24 hours. During the administration of digitalis, electrocardiograms were taken. When the electrocardiogram had attained a stable form, potassium iodide was given again and records were taken daily. After receiving 2 gm. of potassium iodide three times a day, he suffered a low-grade fever and an iodide dermatitis.

Electrocardiograms. After the patient had received 1.8 gm. of digitalis, an electrocardiogram was taken. In this record (Fig. 4, *a*), as well as the electrocardiogram while he was maintained on 0.2 gm. of digitalis daily (Fig. 4, a^1), the *T* waves were diphasic in Leads I, II and IV F, and the R–T segments depressed, changes characteristic of digitalis effect as described by Stewart and Watson.[16] These two records were similar in form and served as controls. The heart rate was 100 per minute.

After receiving potassium iodide for 1 day only, T_1 and T_2 increased slightly in negativity. One left ventricular premature contraction was recorded in Lead III (Fig. 4, *b*). After 3 days on potassium iodide, marked changes were observed. The *T* waves increased in amplitude in all leads and

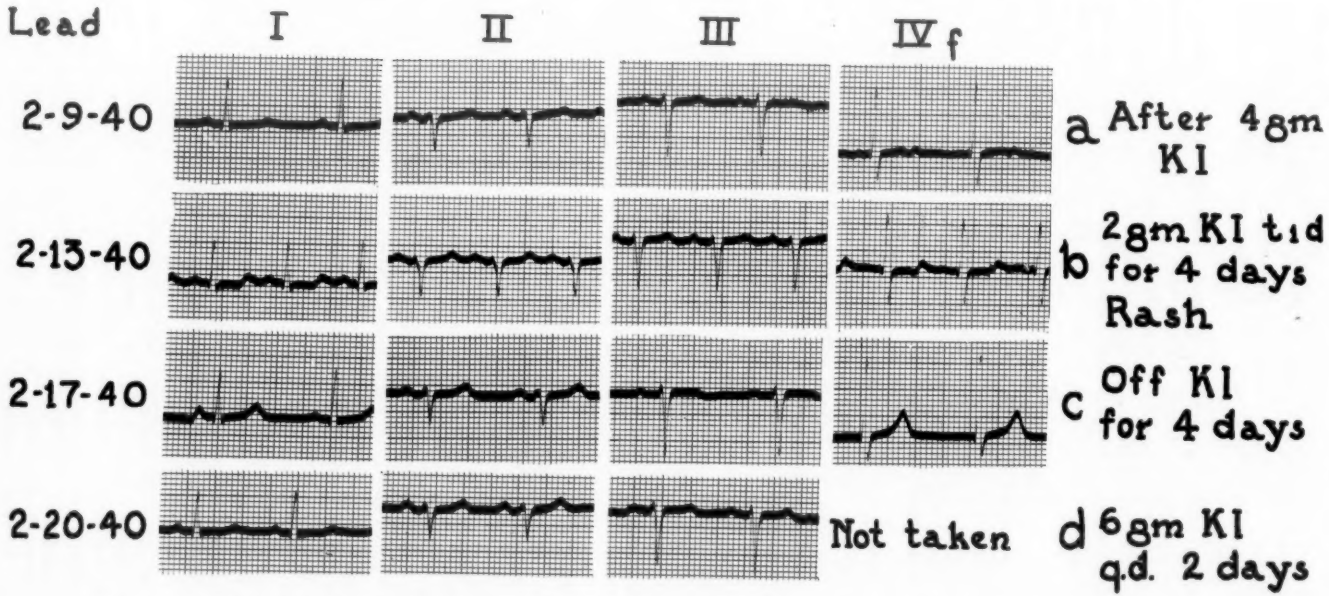

FIG. 2.—In this figure the electrocardiograms of J. L. (Case 2, Hist. No. 131140) are reproduced. For description see text.

R–T_1, R–T_2 and R–T_4 were much more depressed, R–T_3 now slightly elevated and a prominent Q_4 was present (Fig. 4, *c*). The heart rate increased to 125 per minute. When the drug was discontinued the electrocardiogram reverted to the form (Fig. 4, *d*) it exhibited before potassium iodide was given (Fig. 4, a^1).

In this patient suffering from hypertension, emphysema, chronic bronchitis and mild congestive heart failure, the administration of potassium iodide induced tachycardia and alterations in the form of the T waves and R–T segments of the electrocardiogram which are usually thought to be associated with recent coronary occlusion. These changes were reproduced on a second occasion when potassium iodide was given. Iodide rash also occurred.

CASE 3.—A. M., Hist. No. 252085, a male, aged 48, was admitted to hospital on December 6, 1939, complaining of dull pain in the chest and back for 2 weeks. The patient had a chancre in 1920. Sometime later, because of a "positive blood test," he was given 5 "intravenous injections." Two years before admission he first experienced mild exertional dyspnea which increased until he could climb only two or three flights of stairs without discomfort. At rest in bed the patient was not dyspneic. The heart was enlarged; a short blowing diastolic murmur heard over the base and transmitted down the left sternal border was evidence of aortic insufficiency. There were no signs of congestive heart failure. There were no abnormal neurologic findings. Kline and Wassermann reactions of the blood and spinal fluid were negative.

Course. The patient was given 2 cc. of potassium iodide solution (2 gm. KI) three times daily from December 9, 1939, until his discharge on December 19, 1939. Electrocardiograms were taken before, as well as at frequent intervals during the administration of the drug.

Electrocardiograms. The first electrocardiogram showed left axis deviation, normal sinus mechanism, the heart rate 71 per minute (Fig. 5, *a*). The P–R conduction time was slightly prolonged to 0.22 second while the QRS time was within normal limits. From the clinical records we were unable to ascertain whether the patient had taken potassium iodide before admission. In the second and thirds leads, the T waves were diphasic and the R–T segments slightly depressed and slightly "coved." The chest lead was essentially normal in contour.

After the patient had received potassium iodide for 4 days, the form of the electrocardiogram underwent several changes (Fig. 5, *b*). The heart rate increased to 94 per minute. The P–R conduction time increased to 0.26 second. In Lead I the T waves decreased in amplitude and T_2 and T_3 as well as R–T_2 and R–T_3 changed form. After the patient had been given the drug for 8 days, these changes progressed (Fig. 5, *c*). The rate was still 94 per minute, and the P–R conduction time increased still further to 0.28 second. In Lead II the T waves increased in amplitude and were more clearly diphasic while T_3 was slightly more negative. Several months later an electrocardiogram was taken after the patient had not received potassium iodide for 1 month. This served as a control (Fig. 5, *d*). The P–R conduction time was normal; the T waves in Leads I and II were no longer diphasic, but had increased in amplitude, and assumed normal configurations.

In this patient with syphilitic heart disease and aortic insufficiency, the electrocardiogram showed a slightly prolonged P–R conduction time. After the administration of potassium iodide in therapeutic amounts, there resulted persistent and progressive first-degree heart block, increase in heart rate and changes in the form of the T waves and R–T segments which at that time were interpreted as due to slow closure of a coronary vessel at the ostium. Several months later, after potassium iodide had been discon-

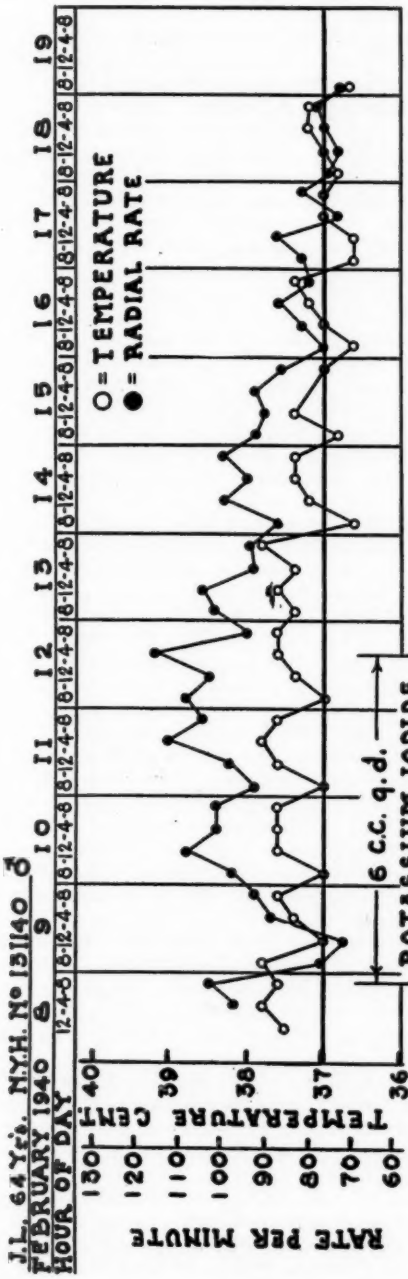
J.L. 64 Yrs. NYH. No 131140 ♂
FEBRUARY 1940
HOUR OF DAY
12-4-8 8-12-4-8 9 10 11 12 13 14 15 16 17 18 19
○ = TEMPERATURE
● = RADIAL RATE
RATE PER MINUTE
TEMPERATURE CENTI.
6 C.C. q.d.
POTASSIUM IODIDE

FIG. 3.—In this figure are reproduced the temperature and pulse records of J. L. (Case 2, Hist. No. 131140). The association between the administration of KI and tachycardia is apparent.

tinued, these changes were no longer present and the electrocardiogram was essentially normal in form.

CASE 4.—J. G., Hist. No. 85687, a male, aged 46 years, was first admitted to hospital in February, 1935, complaining of shortness of breath on effort for 1 month. This symptom appeared for the first time on extreme exertion. He had experienced no palpitation, nor precordial distress. The patient denied having syphilis but admitted having contracted gonorrhea. The patient did not appear ill. The heart was enlarged to the left. The murmur of aortic insufficiency was heard, and Corrigan pulse, capillary pulse, Duroziez's sign and pistol shot sound were elicited. There were no signs of aortic aneurysm or of congestive heart failure. Blood and spinal fluid Kline and Wassermann reactions were 4+. When the diagnostic studies were completed, the patient was discharged and was followed in the Syphilis Clinic. His course over the 4 years between his first and his present admission was uneventful.

Under therapy, the spinal fluid Wassermann became negative. He remained free of cardiac symptoms. When he visited the clinic on April 28, 1939, the heart rhythm was described as "grossly irregular." On May 5, 1939, the patient was admitted to hospital because he was suspected of having suffered coronary occlusion, although he had experienced no symptoms indicative of this accident. He had occasionally suffered paroxysmal nocturnal dyspnea. There had been no significant change in physical signs of the heart. There was no rise in temperature, no elevation of leukocyte count, no acceleration of sedimentation time, no fall in blood pressure, nor other phenomena to indicate that he had suffered coronary occlusion.

Course. The patient was given potassium iodide, 2 cc. (2 gm. KI), three times a day beginning on May 8, 1939, the amount being reduced to 1 cc. three times a day on May 20, 1939. In addition, he received weekly injections of bismuth salicylate in oil. On May 23, 1939, after he had been given potassium iodide, 6 gm. a day for 12 days and 3 gm. a day for 3 days, he complained of rapid beating of the heart. An electrocardiogram was taken (Fig. 6, *c*) which showed transient complete auriculoventricular dissociation. On May 27, 1939, having received potassium iodide for 19 days, he complained of sudden palpitation. Although he experienced distress, it was not characteristic of coronary pain. The heart rate was rapid; the rhythm regular. An electrocardiogram revealed supraventricular paroxysmal tachycardia (Fig. 6, *e*). This attack terminated spontaneously within 5 hours but irregularity recurred 4 days later, May 31, 1939, and on this occasion was found again to be due to transient complete auriculoventricular dissociation (Fig. 6, *f*). Following this episode the administration of potassium iodide was discontinued. It was given again when he returned to the Out-Patient Clinic and once more disturbance in cardiac rhythm occurred. The use of the drug was then discontinued. Sixteen months later, October 7, 1940, the patient remained well, free of cardiac pain and of symptoms and signs of congestive heart failure. An electrocardiogram taken on April 22, 1940, was essentially similar to that recorded on May 1, 1939 (Fig. 6, *a*).

Electrocardiograms. On May 1, 1939, shortly after he had been observed to have a "grossly irregular" heart, normal sinus rhythm prevailed (Fig. 6, *a*). The *QRS* conduction time was increased to 0.11 second, just above the upper limits of normal. T_1 was diphasic, T_2 and T_3 were negative and "coved."

The record taken on May 15, 1939, after the patient had received potassium iodide for 8 days, showed normal sinus rhythm without change in the heart rate (Fig. 6, *b*). T_1 was still diphasic and had increased in negativity, the *R–T* segments had changed slightly in form in Leads I, II and III. The chest lead showed an abnormal configuration of R–T_4 and Q_4 was

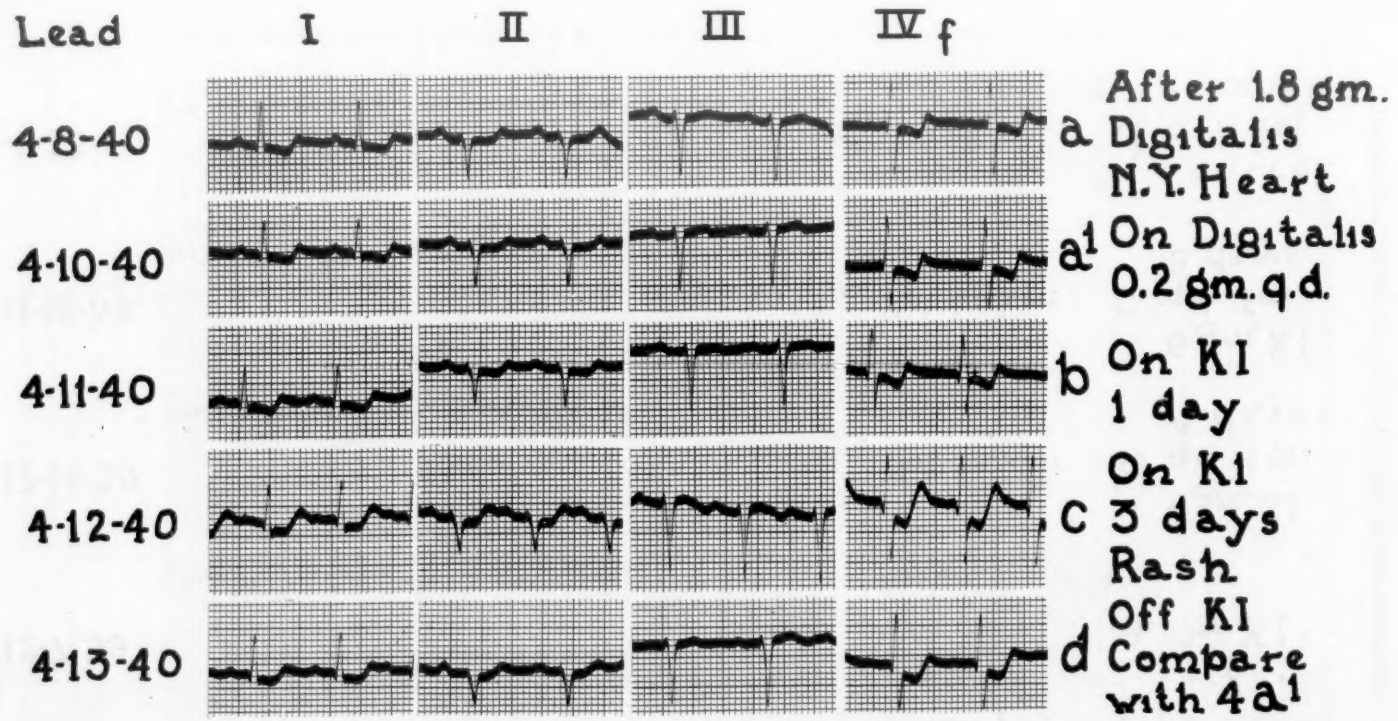

FIG. 4.—In this figure the electrocardiograms of J. L. (Case 2, Hist. No. 131140), on his second admission, are reproduced. For description see text.

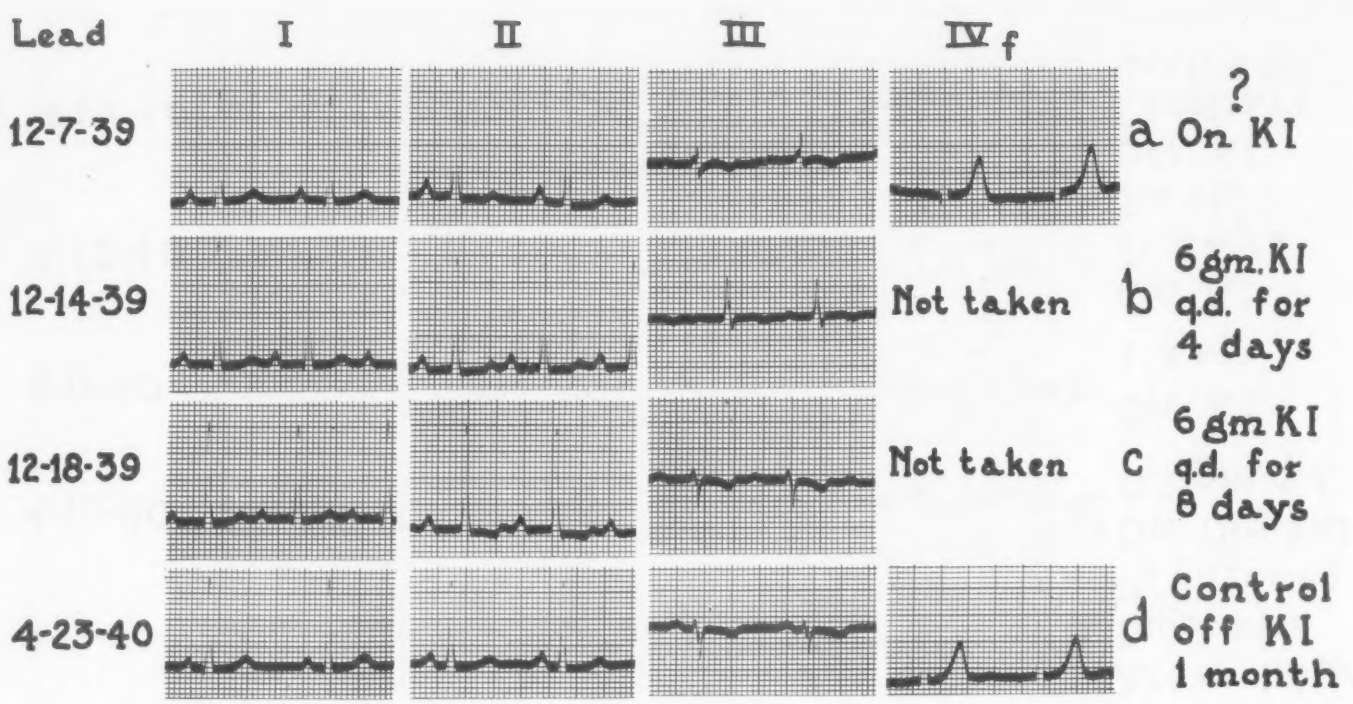

FIG. 5.—In this figure the electrocardiograms of A. M. (Case 3, Hist. No. 252085) are reproduced. For description see text.

present. In the electrocardiogram taken when the patient experienced palpitation, May 23, 1939, the heart rate was 115 per minute (Fig. 6, *c*). The form of Lead I was unchanged. In Lead II there were a few normal beats followed by a short run (6 complexes) of complete auriculoventricular dissociation with irregularity of the ventricular complexes, followed by recurrence of normal rhythm. In addition, the *T* waves in Leads II, III, and IVf had decreased in amplitude and the *R–T* segments changed in form. At that time, it was thought that these changes represented the evolution of the electrocardiogram following recent coronary occlusion.

Three days later, on May 26, 1939 (Fig. 6, *d*), the heart rate was 100 per minute, the rhythm regular. T_2 and T_3 were slightly more negative, T_4 changed slightly in form. When the patient experienced another attack of tachycardia the next day, May 27, supraventricular paroxysmal tachycardia was recorded (Fig. 6, *e*), probably nodal in origin, with the *P* waves buried in the *QRS* complexes. The heart rate was 130 per minute. The electrocardiogram on the following day was essentially of the same form as before tachycardia occurred (Fig. 6, *d*).

Four days later, May 31, 1939, the patient experienced still another attack in which the heart rhythm was irregular. In Leads I and II, there was complete auriculoventricular dissociation (Fig. 6, *f*) with irregularity of the ventricular complexes. In Lead III, block had disappeared and normal sequence restored for 3 beats, followed by recurrence of complete dissociation for 3 beats and then reversion to a normal sequence with prolonged *P–R* time. The administration of potassium iodide was discontinued and the patient suffered no recurrence of arrhythmia. The *T* waves and *R–T* segments now (Fig. 6, *g*) reverted to the form they presented at the beginning of the series (Fig. 6, *a*). While attending the Out-Patient Department, the patient received potassium iodide again sporadically. He suffered attacks of irregularity of the heart and on one occasion, December 29, 1939, there was recurrence of transient runs of complete auriculoventricular dissociation, with irregularity of the ventricular complexes, similar to that recorded in Figure 6, *f*. The patient was unwilling to take the drug longer and it was discontinued. Sixteen months after his last attack of paroxysmal tachycardia, he remained free of symptoms or signs of congestive heart failure without recurrence of irregularity.

This patient with syphilitic heart disease, luetic aortitis and aortic insufficiency, because of alterations in *T* waves and *R–T* segments and occurrence of disturbances of the cardiac rhythm, was thought, at first, to have suffered closure of a coronary ostium. Analysis of his data in relation to the use of potassium iodide, however, showed that these changes were associated with the administration of this drug. In him two abnormalities of rhythm resulted from administration of the drug: transient complete auriculoventricular dissociation, with rapid irregular sequence of the ventricles, and supraventricular paroxysmal tachycardia, probably auriculoventricular in origin.

Case 5.—H. K., Hist. No. 6218, a female, aged 54, had three admissions to the New York Hospital. In 1924, a diabetic régime was instituted when glycosuria was found. Six years later, insulin therapy was begun. When first admitted in 1931, cardiac decompensation and renal insufficiency were discovered. She improved with use of digitalis and other diuretics; diabetes was regulated by diet and insulin and she was discharged 40 days after admission. In April, 1932, she was readmitted to hospital for 5 weeks because of advanced cardiac decompensation.

The patient's final admission, which was of interest in this investigation, was on September 23, 1932. She was dyspneic and had general anasarca. The heart was large; the sounds were distant and of poor quality. There was a rough systolic murmur over the precordium. The blood pressure

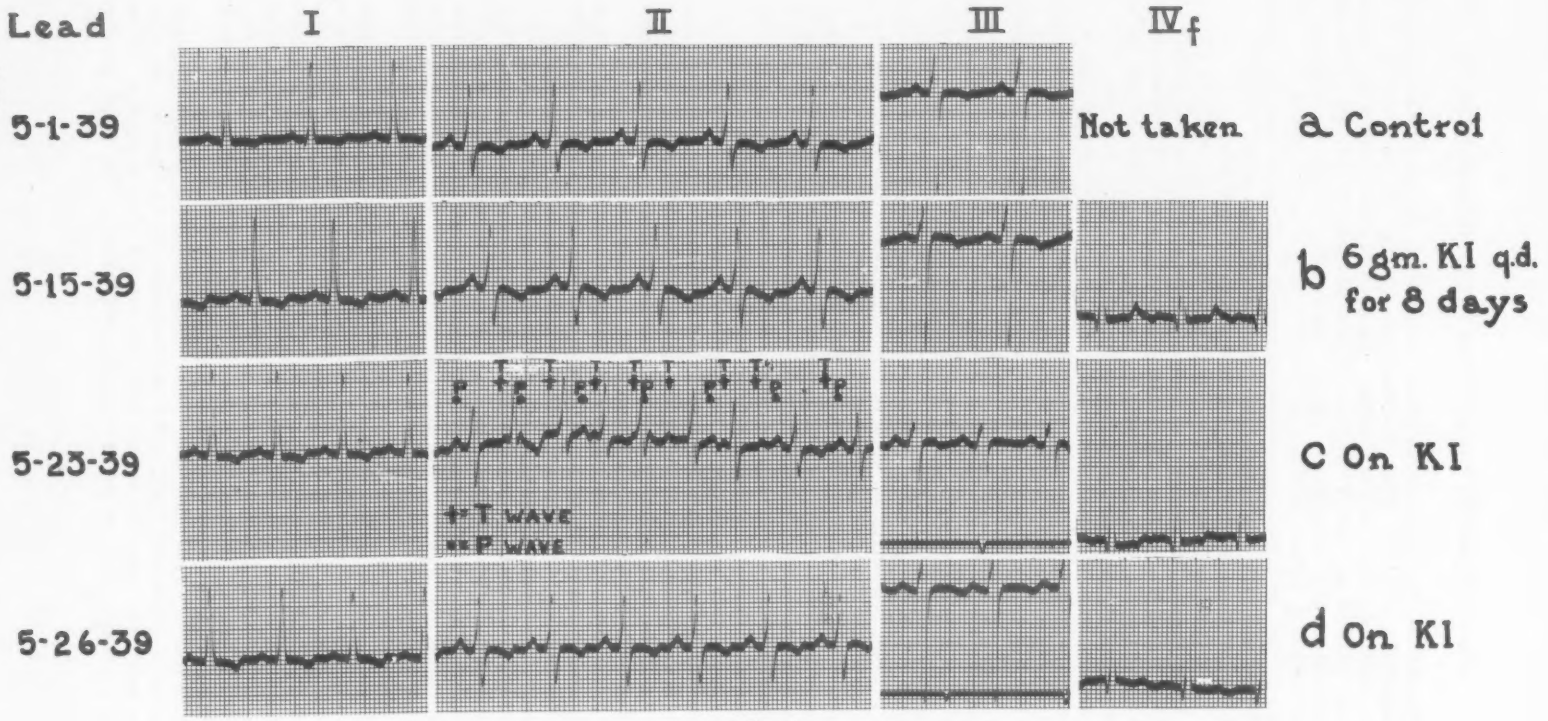
Lead
I
II
III
IV f
5-1-39
Not taken
a Control
5-15-39
b 6 gm. KI q.d. for 8 days
5-23-39
c On KI
+ T WAVE
** P WAVE
5-26-39
d On KI

FIG. 6

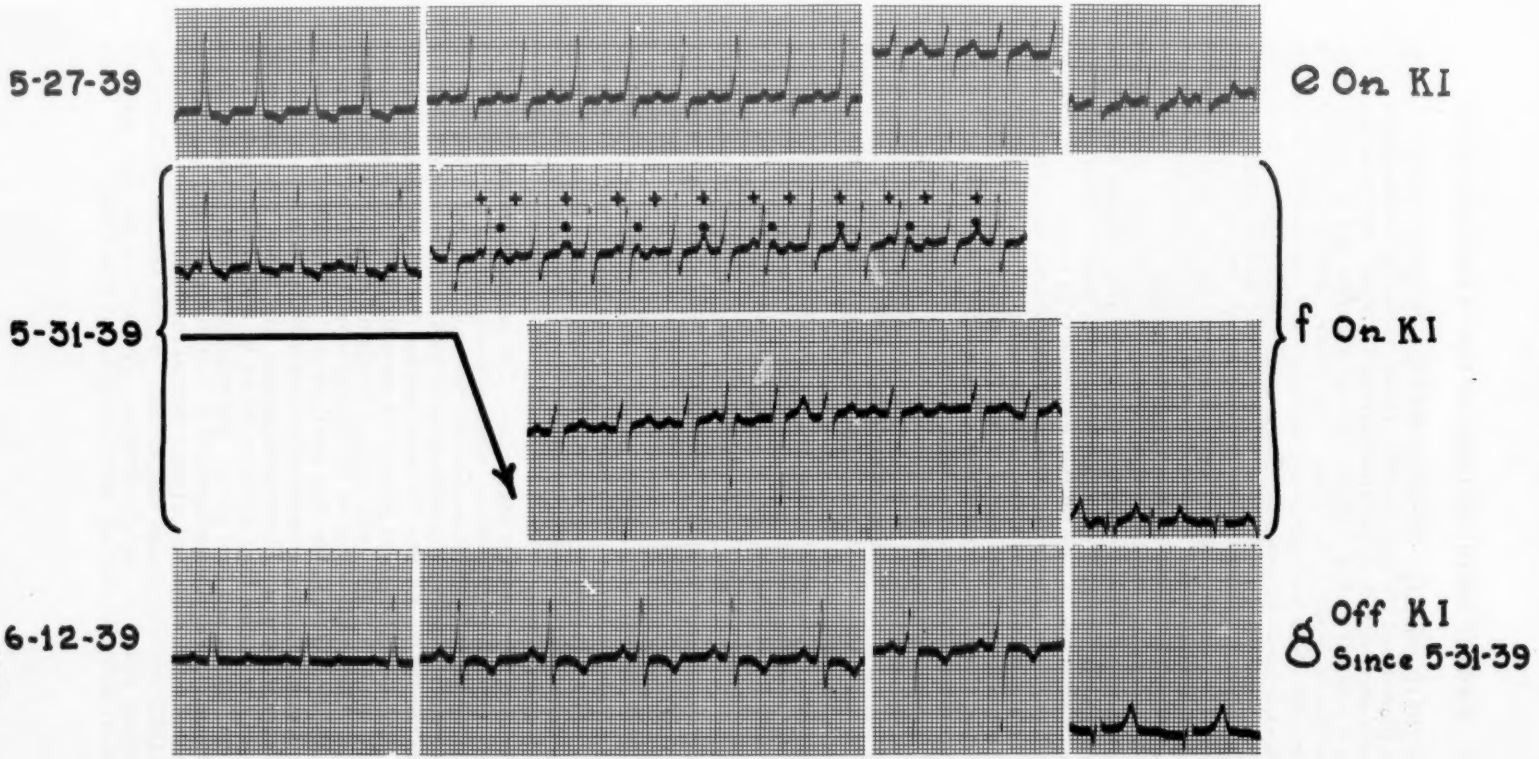

FIG. 6.—In this figure the electrocardiograms of J. G. (Case 5, Hist. No. 85687) are reproduced. For description see text.

was 210/115 mm. Hg. There was fluid in both pleural cavities. Ascites was present and the liver was felt 3.5 cm. below the costal margin. The specific gravity of the urine varied between 1.009 and 1.021 and albuminuria was a constant finding. Glycosuria was moderate and no ketone bodies were demonstrated in the urine. The urinary sediment contained a few white cells and a few hyaline and granular casts, but was free of red cells. There was microcytic anemia. The maximum blood sugar was 254 mg. per 100 cc.; acidosis was persistent with a carbon dioxide combining power which did not exceed 38 vol. % on any occasion. The blood urea nitrogen was 65 mg. per 100 cc., an elevation over the 40 mg. per 100 cc. previously recorded in April, 1932. The phenolsulphonephthalein excretion in 2 hours was 22%. The level of serum proteins was normal.

Course. During the first 3 weeks in the hospital the patient was given a total of 0.5 gm. digitan (Merck). On the twentieth hospital day, an electrocardiogram revealed auricular flutter. The heart reverted to normal sinus rhythm after 1.2 gm. digitan was given in 24 hours.

Although the patient was then given maintenance amounts of digitan, she became progressively worse. The use of insulin was continued; anemia did not respond to the use of iron. The administration of ammonium chloride, theocalcin, theocin, urea (50% solution) and salyrgan did not induce diuresis and edema increased. Two paracenteses abdominis yielded 900 cc. and 2000 cc. respectively. When the congestive failure persisted it was decided to test the diuretic action of potassium chloride. The patient received 5 gm. of potassium chloride daily for 3 days and 2.5 gm. on the fourth day. On the fifth day, 8 gm. were given. Several hours later the patient suddenly appeared to be ill, complained of weakness, fatigue and drowsiness. She was not dyspneic nor cyanotic; respirations were only slightly labored. The radial pulse rate was now found to be *36 per minute*. On auscultation the ventricular beats occurred regularly. Each systole was accompanied by three sounds which suggested the presence of intraventricular heart block with an asynchronism of the ventricles. The patient was given adrenalin intramuscularly without effect on the heart rate. The intravenous administration of calcium chloride increased the cardiac rate to 45 per minute for approximately one-half hour. The oral administration of barium chloride was without apparent effect on the irritability of the ventricular muscle and the patient died, approximately 7 hours after the onset of bradycardia. Electrocardiograms were taken at frequent intervals after the onset of bradycardia and during the use of the emergency measures which were employed.

Permission for autopsy was granted. The pathologic report was as follows: General arteriosclerosis, nephrosclerosis, cardiac hypertrophy and dilatation, chronic passive congestion of the lungs, liver, spleen and kidneys. There was general anasarca with ascites of 2500 cc., and each pleural cavity contained 750 cc. of fluid. The heart weighed 560 gm.; the coronary arteries were patent throughout, although in places the lumen was small. Microscopic section revealed small areas of localized hemorrhage in the muscle tissue. Microscopic section of the kidneys showed advanced thickening of the blood vessels, and less than one-third of the glomeruli appeared to be functioning. Many glomerular tufts showed fibrous replacement.

Electrocardiograms. Electrocardiograms, which are not reproduced, showed the change from auricular flutter to normal sinus rhythm after 1.2 gm. digitan had been given. Maintenance amounts of digitalis were continued. An electrocardiogram (Fig. 7, *a*), taken at this time, served as a control for our present analysis. Normal rhythm prevailed. The *P–R* and *QRS* conduction times were normal. T_1 was negative, R–T_1 slightly depressed and R–T_3 slightly elevated. The form of the *R–T* segments probably indicated coronary artery changes, but from comparison with an

earlier record had been altered slightly by digitalis. On the fifth day after receiving potassium chloride, when the heart rate suddenly fell to 40 per minute, the *R–R* intervals in the electrocardiogram varied from 1.20 to 1.84 seconds (Fig. 7, *b*). Evidence of auricular activity could not be detected either in the three standard leads or in a chest derivation over the auricular projection on the chest. The ventricular complexes were grossly deformed, QRS_1 was greater than 0.24 second, and the duration of electrical systole was 0.70 second. It appeared that auricular standstill had occurred, a site in the left ventricle (old terminology) assuming the function of the pacemaker. That there was widespread interference with conduction was shown by the greatly prolonged *QRS* time, and the bizarre contour of these complexes. Adrenalin hydrochloride, 1 cc., intramuscularly produced no change in the form of the electrocardiogram or in the heart rate. Slight variation in the amplitude and form of the *QRS* complexes was probably due to differences in the pathway of excitation waves through the ventricular muscle.

Following the intravenous injection of 0.5 gm. of calcium chloride (Fig. 7, *c*), the heart rate rose to 45 per minute, the duration of electrical systole remained 0.7 second. A change in sequence of the *QRS* complexes occurred, so that they were now coupled, the shorter *R–R* intervals being 0.96 second and the longer ones 1.68 seconds. The ventricular complexes appeared to arise from the same site and the excitation wave to follow essentially the same course. The administration of barium chloride (0.03 gm.) by mouth effected no marked change. An electrocardiogram (Fig. 7, *d*) taken approximately 3 hours before death showed the same essential configuration, with the exception that the sequence of the *QRS* complexes was totally irregular.

In this patient who suffered from arteriosclerotic heart disease, nephrosclerosis and hypertension, the electrocardiogram taken after the administration of moderate doses of potassium chloride showed an absence of auricular activity. There was no deformity of the *QRS* complexes suggesting that *P* waves might be concealed in them nor was there any deformity when the *QRS* complexes occurred prematurely nor was there evidence of *P* waves or fibrillation waves in pre-auricular chest derivations. The use of adrenalin and barium induced no change. Calcium chloride increased the rate slightly and gave rise to coupled rhythm. The excitation waves appeared to arise in the left ventricle (old terminology). The form of the *QRS* complexes suggested that the excitation wave passed over devious pathways in being conducted through the ventricles.

Discussion. The experimental and clinical data which have been accumulated indicate the important part potassium plays in the physiology of heart muscle. We have observed effects in the electrocardiogram which were clearly to be attributed to this ion. Bizarre electrocardiographic changes during the paralytic phase of familial periodic paralysis appeared to be associated with low serum potassium concentration.[17] We have now reported certain consequences of the therapeutic use of potassium salts in 5 patients. These patients exhibited tachycardia, paroxysmal tachycardia, bradycardia and iododerma as clinical manifestations of potassium toxicity. Moreover, certain electrocardiographic changes were observed. Sinus tachycardia was the simplest effect of potassium iodide on the heart, appearing in 4 cases. The heart rate returned to normal limits when administration of the drug was discontinued.

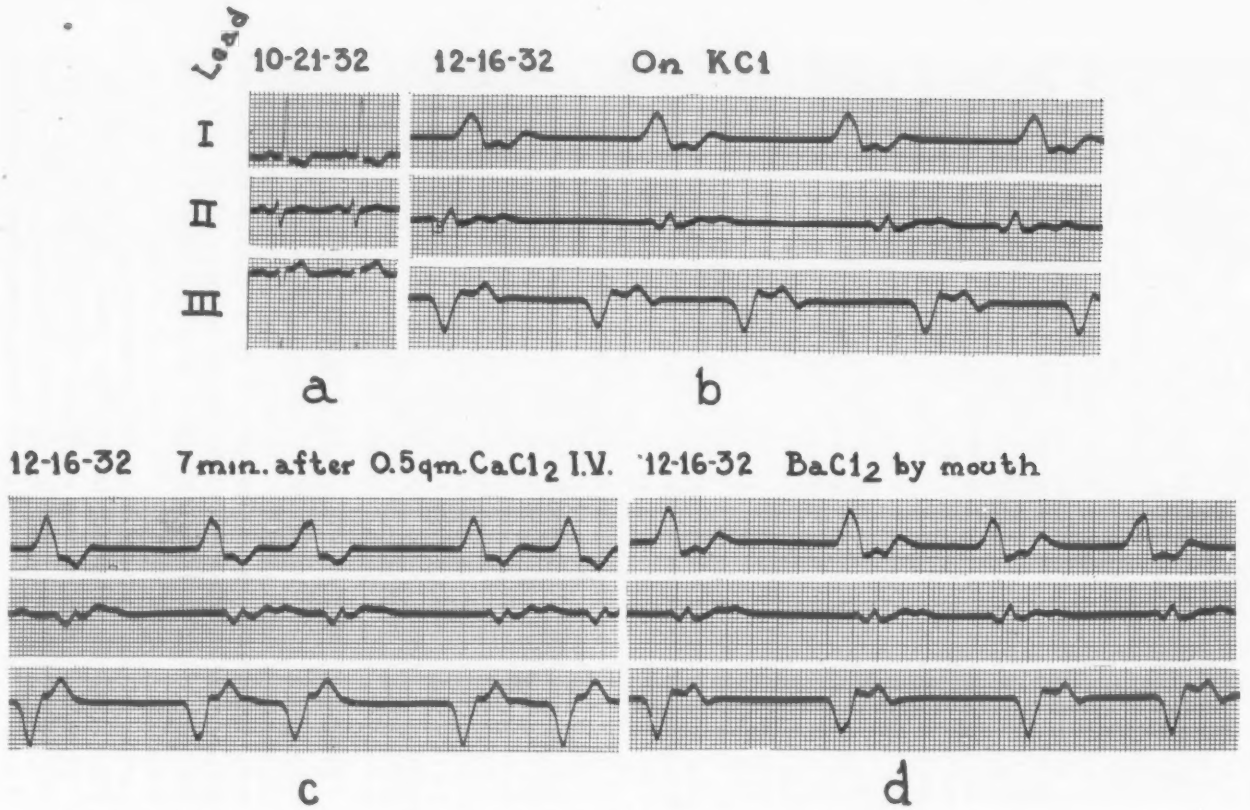

FIG. 7.—In this figure the electrocardiograms of H. K. (Case 6, Hist. No. 6218) are reproduced. For description see text. Pre-auricular chest derivations are not reproduced since they did not show evidence of auricular activity.

In 1 case (J. G., Case 4), the continued administration of potassium iodide induced complete auriculoventricular dissociation with irregularity of the ventricular complexes on 3 occasions. These electrocardiograms were somewhat similar to those which Nahum and Hoff[9] and Chamberlain, Scudder and Zwemer[4] published of ventricular fibrillation in cats resulting from potassium. On another occasion, supraventricular tachycardia, probably auriculoventricular (nodal) in origin, occurred in this patient. Thomson[18b] also encountered this rhythm in his series. In A. M. (Case 3), persistent first-degree heart block occurred during the administration of potassium iodide. After the drug had been discontinued, the *P–R* conduction time fell to 0.16 second.

The changes in *T* wave now being reported differ from those recorded in patients suffering from Addison's disease in whom the concentrations of serum potassium is high. In them, the *T* waves are of increased amplitude and revert to normal with decrease in the level of serum potassium under cortin therapy. On the other hand, in the cases now being reported, the changes occur in the *R–T* segments and changes in amplitude may not be prominent. Our findings are in general agreement with those of Thomson.[18b] Our patients were receiving the usual therapeutic dose of potassium salts, which is somewhat smaller than those given in the clinical observations which have been previously reported and proportionally smaller than those administered to animals. The presence of organic heart disease in these subjects may account for the ease with which toxic effects on the heart appeared.

Two of 3 patients suffering from luetic heart disease, A. M. (Case 3) and J. G. (Case 4), while taking potassium iodide showed changes in the form of the *T* waves and *R–T* segments which disappeared when the drug was discontinued. The changes in *T* waves in the electrocardiograms of these patients were attributed to coronary occlusion before their association with the use of potassium iodide was uncovered. When potassium iodide was discontinued the electrocardiograms reverted in form. In 1 patient (J. L., Case 2), moreover, the *T* waves were changed in amplitude and form when potassium iodide was administered alone as well as when it was given after the patient was digitalized. The early changes in the electrocardiogram of this patient were interpreted as due to coronary occlusion or possibly pulmonary infarction. Since patients with syphilitic heart disease frequently show changes in the electrocardiogram similar to those seen in coronary occlusion, it appears from the evidence now being presented, that some of these cases require reëvaluation. The electrocardiographic effects may be induced by the administration of potassium iodide near the time of recording the electrocardiogram.

Rosenbaum and Levine[11] have called attention to the infrequent occurrence of auricular standstill. In our case, the onset of auricu-

lar standstill was precipitated by the use of potassium chloride as a diuretic. This case is of interest because the sequence of events in the cardiac rhythm duplicated that observed by Chamberlain, Scudder and Zwemer[4] in animals. In 1915, Smillie[14] described the impaired excretion of potassium in the presence of renal damage. In this patient, laboratory and postmortem data revealed advanced kidney disease. The marked renal lesion, no doubt, accounted for the appearance of such severe potassium effects on the heart in view of the relatively low dosage of potassium chloride.

The electrocardiographic changes which have been observed in these 5 patients receiving therapeutic doses of potassium salts are identical with those recorded by Chamberlain, Scudder and Zwemer[4] when they increased the potassium level of the blood in cats (Table 1). Moreover, in the clinic we recorded 1 instance of supraventricular paroxysmal tachycardia which they did not encounter.

Summary. In 5 patients who received therapeutic amounts of potassium salts, we observed electrocardiographic abnormalities which parallel the changes seen in experimental animals receiving proportionally larger amounts of these substances. The following toxic manifestations were encountered: Sinus tachycardia, supraventricular paroxysmal tachycardia, complete auriculoventricular dissociation with irregularity of the ventricles suggesting ventricular fibrillation, progressive first-degree heart block and auricular standstill. These toxic effects with the exception of auricular standstill disappeared with discontinuance of potassium iodide. Three of the 5 patients showed changes in the form of the *T* waves and *R–T* segments which were ascribed to coronary occlusion until their association with potassium was detected. In 1 of these cases, the changes were reproduced a second time after full digitalization. In addition to digitalis (Stewart and Watson[16]), other drugs in common use, namely salts of potassium, are shown to induce electrocardiographic changes which may be confused with those usually attributed to coronary artery disease. Auricular standstill occurred in 1 patient who received potassium chloride as a diuretic. All of the changes we observed have also been observed in experimental animals when the potassium content of the blood was increased.

Because of the widespread use of potassium iodide in the treatment of cardiovascular syphilis and of hypertension, it is not out of place to emphasize that its use is not without danger as these changes in form of the electrocardiogram and in rhythm demonstrate. The most alarming toxic effect in its implications is the occurrence of a rhythm which has certain features similar to ventricular fibrillation. It is possible that certain accidents in patients suffering from syphilitic heart disease in the past may have occurred as a result of toxic effects of potassium on the heart.

Conclusions. From this study certain conclusions may be derived. 1. In addition to digitalis there are other drugs, namely salts of

potassium, which induce change in the T waves and R–T segments of the electrocardiogram that must be taken into account in the interpretation of electrocardiograms.

2. These changes in T waves and R–T segments may be confused with those usually attributed to myocardial damage resulting from coronary occlusion.

3. Rhythms of the heart having serious prognosis may result from the use of potassium salts in therapeutic amounts: (*a*) Complete auriculoventricular dissociation with irregularity of the ventricles simulating ventricular fibrillation and (*b*) auricular standstill.

4. The use of potassium salts may give rise not only to degrees of heart block ranging from prolongation of P–R interval to complete auriculoventricular dissociation, but also to intraventricular block and auricular standstill. These are evidence of toxic effects on the sinus node, and on the specific conducting systems of the heart.

5. These changes with the exception of auricular standstill, so far as can be ascertained from our experience, are reversible.

6. The use of potassium iodide in the treatment of syphilis should be carefully supervised if toxic effects on the heart are to be recognized and their occurrence prevented.

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CARDIAC DISEASE AMONG 28,139 NEWLY ENTERING STUDENTS AT THE UNIVERSITY OF WISCONSIN.

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This group of 28,139 individuals represents all of the new students who were admitted to the University of Wisconsin from July 1, 1931, to July 1, 1939, and each has had the benefit of a complete physical examination. In the event of suspicion or evidence of cardiac or other disease, thorough rechecking of the lesions was carried out.

The literature contains only a few reports on studies concerning cardiac disease in the college group, and Hedley[7] comments that the literature is almost devoid of such material as the incidence of rheumatic heart disease among students in institutions of higher learning. His results are based upon answers to questionnaires sent to colleges and universities in this country (including the University of Wisconsin). Student health services have an exceptional opportunity to collect information and factual material of this nature, although relatively little of it finds its way into the literature.

The vast majority of heart disease in this age group is rheumatic in origin, but there are some few cases that are congenital and a very small number that are due to diseases of the thyroid and other causes.

As I have previously stated, each student is given a complete physical examination, and a careful history of present and past health is recorded. The individual is tuberculin-tested and vaccinated against smallpox (if his vaccination is over 5 years old). If the history is at all suspicious, if it includes rheumatic disease (and particularly rheumatic fever) or if there is a history of heart disease, we give that student an appointment for a recheck examination at an early date. In the meantime he is kept from participation in any sports or activities. The recheck examination is conducted in the quiet of our offices, where we have an opportunity to study the history and suspected lesion in more detail.

Where cardiac abnormality is discovered and the physician wishes consultation, electrocardiographic, orthodiascopic or other confirmatory study, we have the complete coöperation of the Department of Cardiology of the Wisconsin General Hospital.* These studies are made a permanent part of the individual's record and are a valuable addition for future reference and comparison.

Number of Students Examined With Figures Concerning Male and Female Hearts Diseased and Figures on Valvular Involvement. Table 1 represents a summary of students examined and the amount of heart disease found from July 1, 1931, to July 1, 1939.

TABLE 1.—FIGURES ON EXAMINATIONS PERFORMED AND HEART DISEASE DISCOVERED.

Total students examined July 1, 1931 to July 1, 1939	28,139
Total males examined (same period)	18,711
Total females examined (same period)	9,428
Total male hearts diseased	152
Total female hearts diseased	137
Total hearts diseased (male and female)	289
Incidence of heart disease per thousand students	10.2

When the figures in Table 1 are broken down on the basis of diseased hearts among males and among females in reference to their

* The Department of Cardiology is conducted by Dr. C. M. Kurtz, Dr. H. H. Shapiro and Dr. C. S. Mills, to whom acknowledgment is made for their valuable aid in the conduct of these investigations.

relative proportions, it is evident that the incidence among females shows a rather marked preponderance. These figures reveal 1.7 cases of female heart disease to 1 case of male heart disease. The preponderance of female hearts diseased has been a consistent finding in each of these 8 consecutive years.

Thompson and Niehaus[17] have made the observation that while rheumatic heart disease shows a slight increase among female children, its incidence is about equal among adults of the two sexes. Hedley[7] is of the opinion that sex is probably not a major factor in the distribution of rheumatic heart disease among college students. Jones[8] states, in his discussion of the rheumatic child, that early signs of mitral stenosis are more frequent in the female child. It is possible that a larger number of cases collected over a longer period of time may show a somewhat different distribution of sex incidence of heart disease here at the University of Wisconsin.

The average age of the student entering the University with a diseased heart falls between 19 and 20 years.

TABLE 2.—RELATIVE FREQUENCY OF VALVES INVOLVED.

Valve.	No. of cases.	Percentage.
(1) Mitral valve involvement	263	91.0
(*a*) Regurgitation	217	75.0
(*b*) Stenosis	116	40.0
(2) Aortic valve involvement	45	15.5
(*a*) Regurgitation	40	13.8
(*b*) Stenosis	5	1.7
(3) Pulmonic valve involvement	2	0.7
(*a*) Regurgitation	0	0.0
(*b*) Stenosis	2	0.7
(4) Tricuspid valve involvement	0	0.0

Table 2 shows the incidence of valvular involvement and is in keeping with figures quoted by other investigators. These results agree with the observations of Wilson,[18] Cleland,[4] Christie[3] and Cahan[2] concerning the relative frequencies of these particular valvular lesions, and it is thoroughly established that the mitral valve is involved in more than 85% of the cases and is followed next in order by the aortic valve. There is little clinical evidence in the great majority of cases of tricuspid and pulmonic valve involvement except in those cases where the tricuspid may show relative insufficiency (almost always a terminal or near-terminal event). However, autopsy reports reveal a considerably greater number of tricuspid valves involved in the rheumatic process and an occasional pulmonic valve, as noted by Wilson,[18] Cleland,[4] and Bland, White and Jones.[1]

In a study of rheumatic heart disease among children, Seham, Shapiro and Hilbert[15] have found in a group of 379 cases of organic heart disease that 74% were rheumatic, 18% congenital, 3.6% due to other causes, with 4.4% undiagnosed as to cause. They also state that in their group 92% of the cases of early mitral disease had historical evidence of rheumatic infection.

Congenital lesions were recorded as present in 8 cases in this group studied. Congenital cardiac disease predisposes to other heart involvement, and hypertension, subacute bacterial endocarditis and others are examples of these circulatory disabilities.

Table 3 shows the incidence of cardiac hypertrophy, hypertension and evidence of pericardial changes.

TABLE 3.—NUMBER OF CASES OF HYPERTROPHY, HYPERTENSION AND PERICARDIAL DAMAGE.

	No. of cases.	Percentage.
Cardiac hypertrophy	92	31 8
Hypertension*	46	15 9
Pericardial changes	17	5 8

* Cases were considered hypertensive if the systolic pressure was 150 mm. Hg or over, or the diastolic reading was 95 mm. Hg or over.

Cardiac hypertrophy was determined both by clinical means and by orthodiascopy. The orthodiascopic method has the considerable advantage of revealing the adequacy of the retrocardiac space which is of prognostic significance, we feel.

The orthodiagram has been a valuable record for our purposes because it reveals facts not clinically available, such as the frontal area, an accurate frontal diameter, the length of the left auricular salient and, in addition to the retrocardiac space, it gives evidence of certain congenital deformities and significant contour details.

Blood pressure readings have been given a somewhat greater latitude than are commonly allowed. The students are excited, due to the novelty of the experience of college matriculation; late hours are common because of the many social engagements during the first few days of college life; and nervousness concerning the examination with its attendant procedures all contribute to higher than normal readings, we feel. I believe that many of them would be considerably lower if taken 4 to 6 weeks later. Studies of blood pressure include kidney investigation, search for foci of infection, thyroid changes, eye-ground examinations, blood chemistry and Wassermann determinations.

Pericardial changes were noted in 14 cases and represented old insults to the pericardium. (One of these patients developed a large pericardial effusion after an exacerbation of an old rheumatic condition while enrolled in the University.) A history of pericardial effusion was significant, and the laboratory was of great importance in studies of these patients where our clinical findings were not conclusive.

Electrocardiographic Findings. The electrocardiogram is the least valuable of the available methods for study of heart disease in this college-age group and relatively few cases show disorders of rhythm. Friedlander[6] has stated that 33 out of 100 rheumatic hearts revealed changes, and Stroud, Goldsmith, Polk and Thorp[16] comment upon

auricular fibrillation as a terminal complication in rheumatic heart disease. Fibrillation was rare in our group. Sinus arrhythmia was noted in 87 cases but should not be regarded as a pathologic finding. The total number of electrocardiograms made was 145 and only 11 of them showed evidence of pathologic changes as auricular fibrillation, flutter, changes in *T* waves and auricular-ventricular block.

Social, Economic, Geographic and Other Influences. In view of the wide selection of students at this University, all classes of population are represented. There are a number of references in the literature as to the influence of socio-economic factors on the incidence of rheumatic heart disease. Paul and Leddy[12] at Yale showed the incidence to be 8.2 cases per 1000 in their college group, as compared to 15 per 1000 which is given as the average incidence for the same age group in other walks of life. Paul, Harrison, Salinger and DeForest,[13] in a survey of New Haven school children, observed that social circumstances had a definite influence upon rheumatic heart disease, the poorer groups showing the greater incidence of disease.

Coleman[5] reported on some figures given by Brewer who stated that 1 in 200 children in the group studied suffered from an active inflammation of the heart, and Richter[14] states that about 2% of the 91,000 children in San Francisco are cardiac suspects. Nichol[11a,b] showed the inequality of distribution of rheumatic heart disease in the United States and calls attention to the relative infrequency of rheumatic fever and rheumatic heart disease in Florida and subtropical climates.

Maddox[10a,b] reports on a comparison of urban school groups with suburban and rural groups and notes the incidence of rheumatic heart disease to be lower in the metropolitan groups.

Levine[9] calls attention to alteration of internal environment and our glands of internal secretion as possible factors in etiology.

The influence of climate and weather is quite evident in our therapy when we advise those with rheumatic disease to seek a warm, subtropical climate, and repeatedly warn patients against exposure to inclement weather and respiratory infections.

Summary and Conclusions. 1. A group of 28,139 students at the University of Wisconsin was given the benefit of complete physical inventory and examination at the time of their admission between 1931 and 1939, and 289 of them were found to have heart disease. Thus, the incidence of cardiac disease in this age group was 10.2 per 1000.

2. The relation of female to male heart disease was 1.7 females to 1 male, which is a higher proportion of females than is commonly observed. Congenital heart disease was reported to be present in 8 patients.

3. The mitral valve was most frequently involved and was clinically diseased in 91% of this series of cases. The next in order was

the aortic valve in 15.5% and there were only 2 cases of pulmonic valve involvement. The tricuspid valve showed no clinical evidence of disease so far as we were able to determine in our group.

4. Cardiac enlargement was shown to be present in 31.8% of the patients and 15.9% had elevated blood pressures.

5. Pericardial changes were noted in 14 cases (4.8%).

6. Disorders of rhythm, as recorded by electrocardiographic methods, were present in 11 cases (3.8%).

7. Approximately 50% of these students had the benefit of electrocardiographic and orthodiascopic investigations.

8. More of this type of material as noted by student health services should be reported in the literature in view of the similarity of circumstances and conditions surrounding the various college-age groups. It would be an additional impetus to furthering preventive medical practice.

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TREATMENT OF ADDISON'S DISEASE WITH PELLETS OF SYNTHETIC DESOXYCORTICOSTERONE ACETATE IMPLANTED SUBCUTANEOUSLY.

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Recent reports on the use of desoxycorticosterone acetate by Thorn and Firor,[7] McCullagh and Ryan,[4] and Gordon[3] in the treatment of Addison's disease indicate clearly the necessity for a comparative study of results of treatment with suprarenal extract, with desoxycorticosterone acetate in oil (intramuscularly) and desoxycorticosterone acetate implanted by the method of Thorn[8] along with salt regulation. A number of cases treated by one or another of these methods has been reported.[3,4,7,8]

This communication deals with 3 cases of Addison's disease which have been under observation for a period of from 3 to 8 years. In these cases an opportunity has been afforded to study the relative

values of cortical extract and of desoxycorticosterone acetate in oil or implanted, on the same patient.

Case Reports. CASE 1.—*History.* L. G., a married housewife, of 37, was seen first by me in April, 1937. Her chief complaints were general weakness and fatigue. She had been incapable of even mild exertion for the previous 2 to 3 years. She had noticed that her skin had gradually become brown and she had had a great deal of anorexia, nausea and occasional vomiting. In addition to the complaints of muscular asthenia, gastro-intestinal disturbances and pigmentation of the skin, the patient gave a history of bronchial asthma which started about 10 years ago in New York. She came to California 8 years ago and has had many asthmatic attacks ever since.

Physical Examination.—Physical examination revealed a rather undernourished woman, appearing extremely weak and exhausted. The patient was 4 feet 11 inches (149.9 cm.) in height and weighed only 83 pounds (37.65 kg.) at that time. Her skin showed a generalized brownish pigmentation, almost coffee-colored. There was no pigmentation of the mucous membranes. Heart sounds were of fairly good quality, there was a soft systolic apical murmur present. Blood pressure at this time was 95 systolic, 60 diastolic. Lungs were resonant, breath sounds somewhat bronchovesicular and distant with slightly prolonged respiratory phases. There was diffused tenderness over the lower abdomen. (This case is of particular interest, because of the combination of bronchial asthma and Addison's disease. It enables us to interpret the effect of the treatment upon both conditions. I mention this because some authors[5] have advocated treatment of bronchial asthma with suprarenal extract. Others have advocated the use of potassium salts.[1])

Laboratory Data. The red blood cell count was 5,360,000, hemoglobin content 106%, and white blood cell count 9750, with 56.5% neutrophils, 27.5% lymphocytes, 6.5% eosinophils, 0.5% basophils, and 9% monocytes. The blood non-protein nitrogen level was 31 mg. per 100 cc., blood sugar 81 mg. per 100 cc., cholesterol 148 mg. per 100 cc., serum albumin 4.8%, serum globulin 2.4%. The serum sodium was 309 mg. per 100 cc., serum chlorides as NaCl 395 mg. per 100 cc., and serum potassium 24 mg. per 100 cc. The blood Wasserman reaction was negative. The basal metabolism was −15.

Roentgen Ray. Chest: A moderate hypervascularization was seen throughout both lungs. In a flat K.U.B. the kidneys were in normal position. There was no Roentgen ray evidence of calcification of the suprarenal glands.

Routine urinalysis was negative.

Treatment. The patient was placed on adrenal cortex extract, 3 cc. daily intramuscularly, and sodium chloride therapy by mouth from 10 to 20 gm. daily. The cortex extract administration was at times increased or given on alternate days, and the sodium chloride dosage adjusted according to the patient's requirements. She responded rather favorably to this treatment, but I want to stress the fact that her asthmatic attacks were not influenced at all by the cortical extract. The patient remained ambulant most of the time during the following 2 years, and maintained her weight and strength fairly well. The sodium chloride deprivation test described by Cutler, Power and Wilder[2] was employed as an additional aid in diagnosis in August, 1939. Treatment with desoxycorticosterone acetate in oil (Percorten* Ciba) was instituted on August 17, 1939, and continued under constant observation over a period of 4 months. During this time, dosages

* Provided by courtesy of the Ciba Pharmaceutical Products, Inc., through Dr. R. MacBrayer.

were regulated according to the method of Thorn and the optimum daily maintenance dose was determined. Through personal communication with Dr. Thorn, the pellet requirement of desoxycorticosterone acetate* for implantation was calculated from the optimum daily maintenance dose. Preparatory to implantation, as suggested by Thorn (personal communication), vital capacity and heart measurements were determined, as a precaution against possible future cardiac failure.

On December 9, 1939, 6 pellets of approximately 110 mg. each and totaling 689.8 mg. of the synthetic hormone were implanted in the infrascapular region according to the technique of Thorn.[5] The implantation was performed by Dr. I. Y. Olch at the Cedars of Lebanon Hospital in Los Angeles. A graphic summary of the case over the entire period of study is given in Table 1.

CASE 2.—*History.* H. S., a white man of 41, an attorney, was first seen by me in November, 1937. In the previous 2 years the patient had been admitted to several hospitals for "nervous exhaustion, psychoneurosis and malnutrition." In 1931, he underwent a hernia operation. His chief complaints at the time of the examination were general weakness, loss of weight, indigestion and drowsiness.

Physical Examination. The patient was somewhat undernourished, weighing 151 pounds (68.49 kg.); height, 5 feet 8 inches (172.7 cm.). There were dark brown pigmented areas over the face, neck and shoulders. There were brown pigmented areas over both lips and over the inside of the cheeks and tongue. Blood pressure was 100 systolic, 80 diastolic. Examination of the lungs, heart and abdomen revealed no essential abnormalities.

Roentgen Ray Examination. The adrenal area revealed very dense calcifications over both sides. Intravenous urography showed these calcifications to be just above the upper pole of both kidneys. The urography also revealed a large double kidney on the left side with two sets of calyces and ureters. A Roentgen ray picture of the spine, taken in May, 1936, also showed an "area of calcification in the region of the twelfth dorsal vertebra," the significance of which apparently was overlooked. Roentgen ray examination of the chest, gall bladder and gastro-intestinal tract showed no demonstrable changes.

Laboratory Data. The Wassermann reaction was negative, urinalysis and blood count did not show any essential abnormalities. Blood urea nitrogen was 17 mg. per 100 cc., blood sugar 93 mg. per 100 cc., blood chlorides as NaCl 446 mg. per 100 cc., blood sodium 306 mg. per 100 cc. of serum, and blood potassium 27 mg. per 100 cc. of serum.

Treatment. Cortical extract and regulated salt intake were instituted on November 15, 1937, and continued until August 28, 1939. During this period of treatment, the patient kept his weight and strength fairly constant and was able to pursue his regular activities as long as he followed the prescribed regimen. On several occasions, especially during the hot season, the patient showed signs of an impending crisis, which in each instance was successfully averted by the administration of an increased dosage of the cortical extract and salt. On August 29, 1939, desoxycorticosterone acetate in oil was substituted for cortical extract with the view of determining the efficacy of implanting the crystallized hormone in this patient. This was felt advisable, since this patient was not sufficiently coöperative in following the earlier treatment and, thereby, exposed himself frequently to threatening crisis. Desoxycorticosterone acetate in oil was continued from September 12, 1939, until December 15, 1939 (3 months). During this period, the dosage of hormone and salt intake was regulated by careful observation of the patient's weight, blood pressure, maintenance of physical

* Prepared by the Ciba Pharmaceutical Products, Inc., and provided by Dr. George W. Thorn, Johns Hopkins University and Hospital.

strength and blood chemistry data. On the basis of the daily maintenance level, determined during this period, the pellet requirement was calculated. Heart measurements by orthodiagram and vital capacity were determined. On December 16, 1939, 6 pellets of about 150 mg. each, totaling 686.4 mg. of crystalline desoxycorticosterone acetate, kindly supplied by Dr. Thorn, were implanted in the infrascapular region according to the method of

TABLE I.

Date.	Treatment.	Sodium.		Chlorides as NaCl.		Potassium, blood serum.	Blood sugar.	Weight, lbs.	Blood pressure, mm. Hg.
		Blood serum.	Urine.	Blood.	Urine.				
Case 1.									
April, 1938	Cortical extract and salt	309 311	..	395	..	24	81	82	90/72
May, 1938	Cortical extract and salt	339	..	..	..	..	..	84	95/70
Dec., 1938	Cortical extract and salt	344	..	..	..	24	84	88	95/70
Aug., 15–17, 1939	Cutler-Wilder test	..	..	..	..	..	..	92	
	24-hr. period 2d day salt deprivation	344	910 mg.	454	5.0 gm.	25	..	..	95/70
	4-hr. period 3d day salt deprivation	329	99 mg.	429	0.8 gm.	24	..	..	90/70
Control-case	24-hr. period								
24-hr. period	2d day	336	765 mg.	413	2.5 gm.	23			
	4-hr. period 3d day	329	61 mg.	421	0.2 gm.	23			
Aug. 17, 1939, to Sept., 1939	Desoxycorticosterone in oil, and salt addition	342	..	495	9.5 gm.	14.5	76	96	100/70 95/70
Dec. 9, 1939	Implantation pellets desoxycorticosterone with added salt	336	..	503	..	19.1	..	..	100/70
Jan. 24, 1940	....	339	..	512	..	19.5	80		
May 3, 1940	....	331	..	495	....	23.4	80	96	110/80
Case 2.									
Nov. 15, 1937	Cortical extract and salt	306	..	446	..	27	93	151	100/80
Aug. 28, 1939	Cortical extract and salt	309	..	446	8.9 gm.	23	107	156	105/70
Aug. 29, 1939 Sept. 12, 1939	Desoxycorticosterone in oil, with added salt	344	..	495	6.8 gm.	19.8	91	164	112/80
Dec. 13, 1939	....	332	..	495	..	19.2	96		
Dec. 16, 1939	Implantation pellets of desoxycorticosterone with added salt	342	..	503	..	19.8	98	168	115/90
Feb. 4, 1940									
May 8, 1940	....	336	..	495	..	19	96	165½	118/90

Laboratory data determined by Drs. Zeiler and Hammack and Maner Laboratory.

Dr. Thorn. The implantation was performed by Dr. I. Y. Olch at the Cedars of Lebanon Hospital in Los Angeles. A graphic summary of the case is given in Table 1. After implantation of the pellets, the desired sodium chloride intake was determined empirically by following the patient's weight and blood pressure. The optimum salt intake in Case 1 was found to be from 3 to 6 gm. daily; in Case 2 from 8 to 10 gm. daily.

CASE 3.—*History.* M. B., a white man of 30, was seen first in July, 1932. His past history was uneventful with the exception of occasional colds. There was no history of gonorrhea, syphilis or tuberculosis. The patient's present symptoms began in 1928 and were apparently precipitated by the repair of a rectal fistula. Following this operation, he felt weak for several months, and he noticed during this time a brownish discoloration upon his tongue and lips. A similar brownish discoloration also developed over his entire body, so much so that his friends remarked that he appeared like a colored man. In October, 1930, he was treated in a hospital for about 4 weeks. He vomited a great deal, lost weight and grew progressively weak. He did not regain some of his strength until 2 months later. During 1931, the pigmentation had increased in intensity. On July 22, 1932, the patient had a chill and temperature of 104. There was no associated cough, nasal discharge, nor pains in joints and back. The patient vomited considerably. The temperature subsided the next day, but nausea and vomiting persisted. He was admitted to the Cedars of Lebanon Hospital.

Physical Examination. Patient seemed acutely ill and was quite weak and drowsy. He had a peculiar type of air hunger. Pupils reacted to light and accommodation, tongue was coated, and there were bluish-black patches of pigmentation upon tongue, buccal mucous membranes and gums. Neck: left lobe of thyroid gland somewhat enlarged. Heart was not enlarged, there were no murmurs and no irregularities present. Lungs: resonant throughout, no râles. Abdomen: liver and spleen not palpable. Skin: showed diffuse brownish pigmentation with scattered patches of deeper pigmentation, especially dark over face, nipples, penis, scrotum and hands. Temperature 97, pulse 80, blood pressure 100 systolic, 70 diastolic.

Laboratory Examination. Urinalysis normal, except for positive acetone and diacetic acid. Blood count on admission: hemoglobin 107%, red blood cell count 6,200,000, white cell count 4000, with neutrophils 41%, lymphocytes 53.5%, transitionals and large mononuclears 5.5%. Five days later, after treatment had begun, hemoglobin was 97%, the red blood cell count 5,900,000, the white cell count 6900, with 47% neutrophils, 47.5% lymphocytes, transitionals and large mononuclears 4% and eosinophils 1.5%. Blood Wassermann reaction negative, blood sugar 83 mg. per 100 cc., non-protein nitrogen 33 mg. per 100 cc., Van den Bergh reaction normal. Basal metabolism −16. Test meal showed free hydrochloric acid of 12 and total acidity of 18.

Treatment. The patient was placed on Eschatin, 5 cc. daily, given intravenously and intramuscularly at first, and later 2 to 4 cc. daily intramuscularly. The most striking effect was the immediate relief of the gastric discomfort, cessation of nausea and vomiting, and the return and increase of appetite within the first few days. Not less striking, but somewhat slower was the remarkable influence on the asthenia. Improvement in strength and well being followed within a few days. The improvement in strength was not accompanied by an appreciable change in blood pressure. After being on a dosage of 2 to 4 cc. daily for a few weeks, the patient was able to follow his daily routine of life. In December, 1932, I referred the patient to the Mayo Clinic for confirmation of the diagnosis and treatment, where he was under the care of Dr. A. M. Snell. Physical and laboratory examination there gave no additional information, except a skin biopsy, which showed markedly increased melanin pigment in the basal cell layer of the skin. He was advised to continue the small doses of Eschatin, and in addition, to take sodium chloride, 10 to 15 gm. daily. Since then, the patient has led a normal life. There have been times when he has had a respiratory infection. At these times, his gastro-intestinal symptoms and asthenia would recur, his blood pressure would vary slightly, and increased doses of Eschatin, and sodium chloride were neces-

sary to control these symptoms. Subsequent examination at the Mayo Clinic in June, 1936, revealed his blood pressure to be 100 systolic and 60 diastolic. Roentgenograms of the suprarenal glands and of the thorax showed nothing of significance. The blood urea reading was 30 mg., chlorides 578, sodium 347, and potassium 20.9 for each 100 cc. of blood. As additional treatment at this time, he was instructed in a low potassium diet to be supplemented with 8 gm. of sodium chloride and 4 gm. of sodium citrate daily. It was not felt necessary for him to use injections of cortical hormone, except in emergencies. The patient has been under observation for 8 years. His weight has increased gradually from 132 to 143 pounds, his blood pressure and pigmentation have changed little. Throughout these years, he has carried on successfully in his business, which has taken him on many trips.

This case is thought to represent the latent, or stationary, type of Addison's disease. It seems probable that there must be some functional reserve so far as the adrenal cortex is concerned, or he would not have progressed so satisfactorily.

Case 3 represents successful continuous treatment with cortical extract and salt administration for a period of 8 years, and with the duration of the disease for 12 years. The survival time in this case is one of the longest reported in the literature.[6]

In review, Case 1 was treated from May, 1937, to August, 1939, with cortical extract and regulated salt intake, and from August, 1939, to December, 1939 (4 months), with desoxycorticosterone in oil, and from December, 1939, onwards with implanted desoxycorticosterone acetate pellets (8 months).

Case 2 was treated from November, 1937, to August, 1939, with cortical extract and regulated salt intake, from August, 1939, to December, 1939 (4 months), with desoxycorticosterone acetate, and from December, 1939, onwards with implanted desoxycorticosterone acetate pellets (8 months).

Case 3 has been under treatment since 1932. Since it was possible to maintain this patient in good condition by means of cortical extract and regulated salt intake administration, no change of treatment was attempted.

Cases 1 and 2, who had been restored to some degree of health by treatment with cortical extract and salt administration for the past 3 years, are, at present, 9 months after subcutaneous implantation of the synthetic hormone pellets, able to attend to their duties regularly, and are leading a life of moderately restricted activity. The synthetic hormone implantation resulted in a definite increase in weight and improvement of muscular strength and well being. Tendency to edema was controlled by a reduction of the salt intake. The average requirement of sodium chloride was about one-third of the amount necessary under the cortical extract treatment. The blood pressure, both the systolic and diastolic, was considerably higher under the synthetic hormone treatment. An appreciable decrease of pigmentation was noted in both cases after implantation. The laboratory examinations resulted in a definite increase of the

blood, sodium and chloride levels, and in a marked decrease of the potassium level.

No local or systemic complications followed the implantation of the synthetic hormone pellets.

Summary. Two patients with Addison's disease who had been treated from 2 to 3 years with cortical extract injections and salt by mouth were placed on desoxycorticosterone acetate in oil. After the daily quantity of this substance necessary for satisfactory maintenance had been determined, these patients were subsequently implanted with pellets of crystalline desoxycorticosterone acetate. The implantation of pellets of the synthetic hormone resulted in a gain of body weight, an increase in blood pressure, general physical improvement and return to normal activity. Clinical improvement was associated with a normalization of the blood electrolyte relationship during 10 months of observation.

One patient with Addison's disease was treated over a period of 8 years with cortical extract injections and large doses of salt by mouth. No change of treatment was attempted in this case since this patient's symptoms were adequately controlled in this way.

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THE LOCAL USE OF SULFANILAMIDE POWDER AND HYDROGEN PEROXIDE IN WOUND INFECTIONS.

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There are only a few reports in the literature dealing with the efficacy of sulfanilamide used locally, even though it has been widely employed systemically. Jensen, Johnson and Nelson[8] used it locally in 39 cases of compound fractures as a prophylactic with excellent results. They found that with careful hemostasis, thorough débridement, and primary closure, the introduction of 5 to 15 gm. of powdered sulfanilamide could eliminate complicating infections which were formerly observed in 27% of these cases. They also observed that the sulfanilamide was absorbed readily from the wound, and produced blood concentrations approximating those produced by oral administration. It remains a moot question whether the effect was due to the local concentration of the drug,

to the substance carried to the inflamed tissues *via* the blood stream, or a combination of the two.

Sezary[18] has reported better results with chancroid lesions by the local application of sulfanilamide than by oral administration. Dentists have also reported success in using the drug locally in dry sockets[19] and also in root canal therapy.[1]

Lockwood and Lynch[13] as well as Larson, Bieter, Levine and Hoyt[11] suggest that even small amounts of peptone may greatly reduce the bacteriostatic and bacteriocidal effect of sulfanilamide and its derivatives. King and Henschel[10] found that tissue fragments interfered with the bacteriostatic effect of sulfanilamide on beta streptococci *in vitro*. In the light of these two findings, the wounds in the cases to be described were washed out thoroughly with hydrogen peroxide until they presented a clean appearance. The fact that no beta streptococci could be cultured from either case 16 hours after powdered sulfanilamide had been placed in the wounds indicated that the remaining peptone and tissue fragments, in all likelihood, were insufficient to interfere with adequate bacteriostasis.

Fox[7] found that increased oxygen availability increased the bacteriostatic action of sulfanilamide, whereas reducing agents decreased its effect. Main, Shinn and Mellon[15] showed that sulfanilamide has an anticatalase activity which prevents the destruction of the hydrogen peroxide produced by the organisms. This allows the hydrogen peroxide to reach a high enough concentration to prove toxic to the organisms. Mellon, Locke and Shinn[17] give added support to the oxidative-enzymatic theory of the mode of action of sulfanilamide. They find that the free amino group of sulfanilamide when incompletely oxidized is responsible for the anticatalase activity exhibited by the drug. The fact that the streptococcus, pneumococcus, gonococcus, meningococcus and *B. coli* organisms all produce hydrogen peroxide is given as the reason for the wide therapeutic applicability of the drug. They suggest that staphylococcic lesions are usually of a reducing nature and do not allow for the oxidation of sulfanilamide to products that exhibit anti-enzymatic activity. It is to be noted that the staphylococci were eradicated with greater difficulty than the streptococci in our cases. It is felt that the hydrogen peroxide helped to overcome the reducing properties present in the wounds.

In view of the above findings, hydrogen peroxide was left in the wounds in our cases, and powdered sulfanilamide suspended in hydrogen peroxide was introduced into the sinuses leading from these wounds. Hydrogen peroxide was used as the oxidizing agent of choice because it was suspected of being the intermediate agent responsible for the toxicity of sulfanilamide to the bacteria.[15] In this manner oxygen availability was increased and the toxic effect of the sulfanilamide on the offending bacteria was potentiated. In

support of this we have some experiments *in vitro* by Fox.[7b] He found that the resultant bacteriostasis produced by the addition of small amounts of hydrogen peroxide to cultures of *strep. hemolyticus* containing 10 mg. of sulfanilamide per 100 cc. of media was more than ten times greater than the bacteriostasis produced by corresponding amounts of sulfanilamide used alone and more than two hundred times greater than that produced by equal quantities of hydrogen peroxide used alone.

The total amount of sulfanilamide which would usually be given by mouth in 24 hours was placed in the wound at one time, and this was replenished daily. Thorough cleansing allowed intimate contact with the absorbing surface. All recesses and sinuses were flushed with the suspension of sulfanilamide in hydrogen peroxide. Lawrence[12] reported a case of chronic undermining streptococcal ulcer using a total of 8400 gr. of sulfanilamide orally to obtain a cure. In our case of a similar type with more extensive involvement we used a total of only 570 gr. locally.

Because of the high blood sulfanilamide concentrations resulting from this mode of administration, all of the toxic manifestations produced by oral administration may also be expected here. It is possible that high local concentrations may prove toxic to the tissues. However, no ill effect was noted locally in either of the 2 cases presented. In the case of chronic periostitis it is of interest to note that the patient developed an alopecia of the scalp which proved transient. She also developed a papulovesicular rash of the palms of both hands and the soles of both feet. Both of these toxic symptoms are a general manifestation of the drug. Local areas of alopecia in rats receiving sulfanilamide over long periods of time have been observed by Antopol, Goldman and Sampson.[2]

Bricker and Graham[4] found a delay in healing of abdominal wounds in dogs receiving sulfanilamide by mouth. Key and Burford[9] found that experimental fractures of the forelegs of rabbits healed just as well with sulfanilamide in the wound as without it. In our cases healing continued at a rapid pace at a time when the wound was thoroughly saturated with sulfanilamide.

Many modifications suggest themselves. It is possible that the local use of sulfanilamide with zinc peroxide might prove efficacious in the treatment of chronic undermining ulcers due to the microaërophilic hemolytic streptococcus, one of the organisms present in Case 1. Meleney and Harvey[16] found that the combination of zinc peroxide used locally and sulfanilamide orally was more effective in such cases than either alone. The possibility also suggests itself that it might be an effective treatment for acute and chronic osteomyelitis. The organisms encountered in our 2 cases are similar to those found in osteomyelitis. Besides, as can be seen in the accompanying illustrations, complete healing of the osteoperiostitis ultimately was achieved.

Case Reports. CASE 1.—R. N., a 16-year-old white female was first admitted, April 9, 1938, for a soft tissue swelling at the lower end of the right thigh, which on later admissions proved to be an abscess resulting from a chronic periostitis. She was admitted 5 times during the next 2 years, spending a total of 26 weeks in the hospital. Wound cultures on those occasions revealed hemolytic streptococci. Treatment consisted in curetting the bone and incising the abscesses, but always she returned with new collections of pus and other sinuses.

Present Admission. September 27, 1939, to June 7, 1940.

Chief Complaint. Pain along inner aspect of right thigh, 2 weeks' duration. Fever of a few days' duration.

Physical Examination. Grayish-brown discharge from sinuses of right thigh. Otherwise negative.

FIG. 1.—Case 1. February 10, 1939. Lower end of right femur showing early periostitis.

Laboratory. Temperature, 103°. Roentgen rays: Periostitis with cortical necrosis, reported by Dr. N. J. Furst, Chief Roentgenologist. Wound culture: *Staph. aureus hemolyticus, Strep. hemolyticus* of the micro-aërophilic type.

Course. Over a period of 10 weeks various forms of treatment were tried unsuccessfully. The yellowish-gray discharge became more profuse and the sinus tracts deepened. On December 14, 1939, an operation was performed in which the sinus tracts were widely excised, the bone curetted and a through and through rubber drain was placed between the lower end of the femur and the hamstring muscles.

Immediately after operation her temperature rose sharply to 105° and a tremendous greenish yellow purulent discharge poured out of the wound. Dakin's tubes were inserted and continuous irrigation with azochloramide, 1 to 3300, was accomplished through them. The skin flaps became very tender, there was marked itching of the entire leg and in less than 2 weeks the skin became undermined to within 2 inches of Poupart's ligament. At this time the wound extended for three-quarters of the length of the thigh. Wound culture on January 4, 1940, showed *Staph. aureus* and *Strep. hemolyticus*. Three days later, a severe hemorrhage from one of the sinus tracts caused the patient to go into shock. A transfusion was given and the tract

FIG. 2.—Case 1. October 10, 1939. Same, showing osteoperiostitis 4 months before institution of local sulfanilamide and hydrogen peroxide therapy.

packed tightly. At this time, azochloramide was discontinued and gentian violet, 5%, was used in the wound in its stead. During the next month, she had 3 other exsanguinating hemorrhages. At the time of the last hemorrhage she became unconscious and her respirations became Cheyne-Stokes in character. Shortly afterwards foot drop and toe drop developed, along with marked edema of the entire extremity from the knee down. Metastatic sinuses developed about the heel and ankle. One of these caused an area about 3 inches long and 1 inch wide to sluff away, exposing the upper part of the tendon of Achilles. In addition to the other organisms previously encountered, *B. pyocyaneus* was now cultured from the wounds of the thigh and ankle. Acetic acid 1%, used continually for 1 week failed to diminish the effect of this organism.

On February 17, 1940, after the wound had been thoroughly cleansed and flushed with hydrogen peroxide and under sterile technique, sulfanilamide powder (4 gm.) was packed under the skin flap and placed on the granulations. Sulfanilamide powder (2 gm.) was suspended in 30 cc. of hydrogen peroxide and this suspension was introduced into the sinuses. Many gauze dressings were used to cover the wound. In 24 hours the granulations appeared healthy for the first time, the discharge became about one-fourth of what it previously had been, and the tenderness had disappeared. This treatment was repeated for 4 days in succession in the

FIG. 3.—Case 1. May 20, 1940. Same, showing healing osteoperiostitis 3 months following local sulfanilamide and hydrogen peroxide therapy.

wound on the thigh. But slight improvement was noted in the draining sinus at the ankle. Cultures from it were still positive for all the organisms as before, whereas those from the thigh were only positive for *B. pyocyaneus*. When the above treatment was applied to the ankle wound, it too improved. Since that time, in spite of the presence of *B. pyocyaneus*, the wounds steadily healed and the sinuses closed. Cultures remained consistently negative for all organisms except *B. pyocyaneus* until the wound had completely healed.

Two untoward symptoms were noted. The hair on the patient's head began to fall out. While this was alarming for a short time, it soon ceased. She also developed a papulo-vesicular eruption of the palms and soles of both hands and feet. This slowly disappeared over a period of a month, during which time no sulfanilamide was used.

During the last few days of February, the discharge became more profuse and *B. pyocyaneus* was again found to be the offending organism. On February 29, 1940, 6 gm. of powdered sulfanilamide were again introduced after the wound had been thoroughly cleansed with hydrogen peroxide. Within 48 hours the discharge became about one-tenth of what it previously had been. Repetition of the wound cultures at that time revealed that the causative organism was still present, but it appears that some inhibition of its growth had taken place. Blood and urine sulfanilamide determinations were made 16 hours following the above administration of 6 gm. of powered sulfanilamide, and it was found that the free sulfanilamide in the

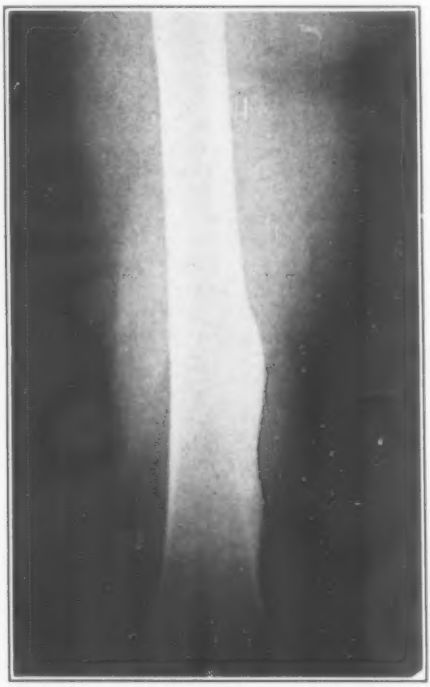

FIG. 4.—Case 1. August 1, 1940. Same, showing complete healing of osteoperiostitic process with complete filling in of all osteoporotic areas.

blood was 5.4 mg. per 100 cc., and the total was 10.2 mg. per 100 cc. Forty hours later the free sulfanilamide in the blood was 2.4 mg. per 100 cc. and the total 4.6 mg. per 100 cc. On March 24, 1940, 4 gm. of sulfanilamide powder were introduced into the wound at a time when it was one-third of its former size. A blood concentration of free sulfanilamide of 1.5 mg. per 100 cc. was found to be present after 16 hours. At 40 hours 0.4 mg. per 100 cc. of free sulfanilamide was found to be present. Four days later 4 gm. of sulfanilamide powder were reinserted and similar blood concentration levels were recorded.

Once a week powdered sulfanilamide was sprayed on the wound by means of a Shelanski insufflator. After each treatment the discharge became noticeably less and the wound gradually closed. By the end of May complete healing had taken place and the patient began walking with the aid of a cane. She was discharged June 7, 1940. A Roentgen ray taken August 1, 1940, revealed complete healing of the osteoperiostitis (Fig. 4).

CASE 2.—H. D., a 19-year-old white male, was admitted March 14, 1940; discharged, April 4, 1940.

Chief Complaint. Infection above right knee following trauma of 1 week's duration.

Physical Examination. Thick brown purulent discharge coming from an opening in suprapatellar region of right leg. The leg was held in a fixed position and there was marked tenderness and spasticity of the muscles of the thigh. The femoral glands were slightly enlarged and tender.

Laboratory. Wound culture: *Staph. aureus hemolyticus* and *Strep. hemolyticus.* Roentgen ray: Negative for bone lesions. Temperature, 101.4°.

Course. After hot wet dressings the temperature subsided. However, the discharge became more profuse and the pain in the thigh became more intense. Because of the lack of improvement in the symptoms, the decision was reached to open the abscess. Eight days following admission, a large intramuscular abscess was incised and packed with 6 gm. of sulfanilamide powder after some hydrogen peroxide had been left in the wound. The following day 4 gm. of sulfanilamide powder, along with hydrogen peroxide, was placed in the wound. Two days following this hemorrhage from a few subcutaneous bleeders took place. These were controlled by ligation. Three days following the original introduction of the sulfanilamide the discharge had ceased completely. Cultures from the depths of the cavity revealed the presence of *Staph. aureus hemolyticus.* Cultures repeated 2 days later were found to be sterile. The wound was brought together with windowed adhesive. The inguinal and femoral adenitis slowly subsided. Twelve days after operation the patient was discharged with the wound healing well by primary union. Free sulfanilamide was found to be present in the blood for 82 hours following its original introduction on successive days. The highest concentration reached was 1.6 mg. per 100 cc. A total of but 10 gm. of powdered sulfanilamide was used.

Summary. 1. Two cases of wound infection with *Strep. hemolyticus* and *Staph. aureus hemolyticus* were treated successfully by repeated local administration of powdered sulfanilamide and hydrogen peroxide.

2. In Case 1 where concomitant bone involvement was present, complete healing of the osteoperiostitis took place.

The author wishes to express his gratitude to Dr. William Antopol, Pathologist and Director of Laboratories, for his sincere advice and criticisms; to Dr. Max Danzis and Dr Eugene V. Parsonnet for permission to use Case 1; to Dr. Bernard H. Greenfield for permission to use Case 2; and to Dr. N. J. Furst for his Roentgen interpretations.

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THE INTRAVENOUS USE OF SODIUM SULFAPYRIDINE IN THE TREATMENT OF PNEUMONIA AND PNEUMOCOCCUS INFECTIONS.*

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In the treatment of pneumonia and pneumococcic infections with sulfapyridine, the oral administration is to be preferred. There are times, however, when for one reason or another the administration by a route other than oral is desirable. This is especially true with those patients who are seriously ill or who are unable to take oral medication. It also applies to those who have not responded satisfactorily to sulfapyridine orally or who cannot be given serum. In such cases an effective concentration of sulfapyridine in the blood may be obtained immediately by the use of sodium sulfapyridine intravenously. It is our purpose in this paper to emphasize the practical importance of this route of administration in the treatment of severe pneumococcic infections and to point out that the advantages are greater than the disadvantages.

Selection of Cases. The material for this study consists of work done on 80 patients with pneumonia selected from a total of 200 admitted to Cook County Hospital between November, 1939, and May, 1940. Their selection was made on the basis of the greater severity of their illness at the time of admission to the service or because they failed to respond to oral sulfapyridine. The causative agent was the pneumococcus in 73 patients, the streptococcus in 3, the *B. Friedländer* in 2, and the etiology was not determined in the remaining 2. Four patients had meningitis caused by the pneumococcus. A summary of the 80 patients treated is shown in Table 1.

* This study has been made possible through the coöperative efforts of the attending faculty at Cook County Hospital.

TABLE 1.—ANALYSIS OF CASES.

	Total.		Coma delirium.		Bacteremia.		Relapse.		Oral S.P. failure.	
	No.	Died.	No.	Died.	No.	Died.	No.	Died.	No.	Died.
Total	80	22*	24	19	37	17	4	0	13	1
Pneumococcus	73	17	19	15	34	14	4	0	13	1
Streptococcus	3	2	3	2	2	2	0	0	0	0
B. Friedländer	2	1	0	0	1	1	0	0	0	0
Unclassified	2	2	2	2	0	0	0	0	0	0

During the past year all patients with pneumonia were given oral sulfapyridine routinely on admission or as soon as the clinical diagnosis was established. In the above group sodium sulfapyridine was used intravenously supplementary to oral sulfapyridine in all except 5 patients who were treated by the intravenous route alone (oral medication was omitted). A total of 115 injections were used. It was not given to patients with a mild or moderately severe pneumonia, or to those who responded to oral sulfapyridine. However, no restrictions were put on its use in critical cases. Often a patient showed signs of a preëxisting disease, or of a complication associated with the pneumonia at the time of admission to the hospital. This added to the gravity of the prognosis. We were aware of the potential toxicity of sodium sulfapyridine, but decided that urgency for treatment of the infection was more important than the possible toxic effect of the drug. Control of the more recent superimposed pneumonia seemed to offer the best chance for recovery. As a result it was used in: (*a*) all patients who appeared terminal with little or no chance of recovery; (*b*) patients whose temperature did not show an appreciable decline within 24 hours after the administration of oral sulfapyridine (Chart 2); (*c*) patients who failed to obtain a level of 4 to 5 mg. per 100 cc. within 24 hours unless the temperature and pulse had returned to normal (Chart 3); (*d*) patients who, because of nausea and vomiting, could not retain, or refused to take oral sulfapyridine (Chart 2, *A* and *B*); (*e*) patients who, after an initial favorable response, had a relapse in spite of continued full dosage of oral sulfapyridine (Chart 3, *A*, *B*, *C*); (*f*) patients with a persistent bacteremia.

Methods. All patients in this series were given sodium sulfapyridine† intravenously; the dose, from 3 to 5 gm., was dissolved just before use in from 50 to 100 cc. of 0.8% solution of sodium chloride or distilled water just below boiling point. It was administered in 10 to 30 minutes, depending chiefly on whether or not the patient was receiving intravenous fluids at the time. When such was the case the solution was injected into the tubing of the infusion or was mixed with the fluid in the infusion flask. When no infusion was being given (approximately one-half the cases) the solution was injected directly into the antecubital vein at a rate of from 5 to 10 cc. per minute. Free sulfapyridine blood levels were determined

* Fifteen patients died within the first 24 hours (see Table 3).

† The sodium sulfapyridine used in this study was made available through the generosity of Merck & Co.

at various intervals after each injection (2 to 12 hours). In 3 patients sulfapyridine levels of the gastric juice were made simultaneously with blood determinations (see Table 2).

TABLE 2.—SULFAPYRIDINE LEVELS OF GASTRIC CONTENTS AND BLOOD AFTER 4 GRAMS OF SODIUM SULFAPYRIDINE INTRAVENOUSLY.

	Before I.V.	5 min.	10 min.	30 min.	60 min.	2 hr.	12 hr.	24 hr.
Case 1 (J. D.):								
Gastric—Free	0	12.5	22.2	23.8	19.6	20.0	8.7	
Total	0	12.8	22.2	23.8	19.6	20.8	9.6	
Blood—Free	0	5.2	..	..	..	2.8	0.7	
Total	0	5.7	..	..	..	3.6	1.8	
Case 2 (H. R.):*								
Gastric—Free	100–0*	24.7	37.0	18.2	5.0	2.9	..	13.5
Total	100–0	25.0	38.0	..	5.0	3.3	..	16.6
Blood—Free	2.27	11.7	..	..	..	7.8	..	16.4
Total	3.2	11.7	..	..	..	9.5	..	21.0
Case 3 (J. G.):								
Gastric—Free	0	4.2	4.2	4.8	6.4	5.9	4.4	
Total	0	4.2	5.0	5.7	6.4	6.3	4.7	
Blood—Free	0	9.8	..	..	7.6	7.6	3.5	
Total	0	9.8	..	..	9.1	..	5.8	

Cases 1 and 2 had nausea and vomiting. Case 3 had no nausea and vomiting.

* Four grams of sulfapyridine were given orally 12 hours before the intravenous salt was administered. The stomach was lavaged until the washings were free of sulfapyridine. Then sodium sulfapyridine was injected.

Toxic Manifestations. No severe toxic reaction was encountered during or after administration of a solution of sodium sulfapyridine. No chills, extreme restlessness, apnea, fall in blood pressure, collapse, muscle-twitching or convulsions occurred. A few patients complained of a mild burning sensation along the course of the vein in the arm. Such symptoms, however, are not uncommon with intravenous medications that are strongly alkaline.

Thrombophlebitis or perivascular reactions were not encountered.

In very toxic or delirious patients sodium sulfapyridine seemed to aggravate the symptoms temporarily, just as did oral sulfapyridine. The incidence of blood dyscrasia or renal damage was no higher in patients who received the intravenous salt than in those who received the oral salt alone.

Of the 80 patients treated, nausea and vomiting occurred in 15; nausea alone in 5 additional cases.

Five patients were treated with intravenous sodium sulfapyridine alone. Each received an injection of 4 gm. at 12- to 24-hour intervals until a satisfactory response was noted. One patient received three injections, 3 received four, and 1 received five. All recovered from their pneumonia. Nausea and vomiting occurred after the first injection in 4 patients. However, after subsequent injections it was mild and of little consequence. Nausea, then, was the chief complaint. In 3 patients who were treated in this manner (Table 2), simultaneous blood and gastric concentrations of free and total sulfapyridine were determined at frequent intervals. The gastric levels in 2 patients (Cases 1 and 2) who experienced nausea and

vomiting were from 2 to 4 times the simultaneous blood levels. This was most marked in the first 30 minutes after the injection and corresponded with the period when nausea and vomiting were most pronounced. With the patient (Case 3), who did not experience nausea and vomiting, the gastric concentration never approximated that in the blood. We were able, also, to confirm the observations of Kinsman[3] that gastric lavage relieved the nausea. The early investigators[5] attributed nausea and vomiting after oral sulfapyridine to gastric irritation, but because it came on so rapidly after injection of sodium sulfapyridine, central irritation was

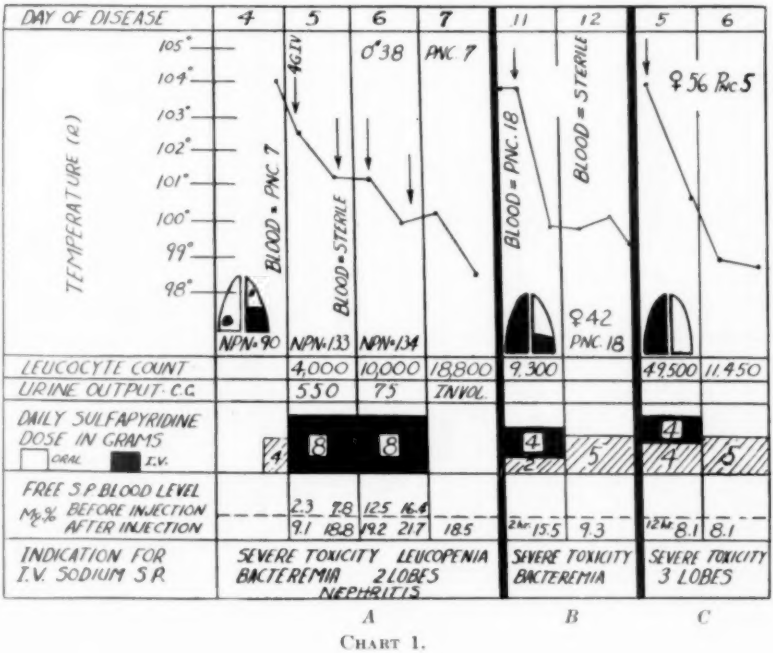

CHART 1.

thought[4] to be a likely explanation. In this series, the onset of nausea and vomiting, however, was not sufficiently rapid to be attributable to irritation of the central nervous system. Further, the fact that the concentration of sulfapyridine in the gastric contents was higher than the level in the blood within a few minutes of the injection suggested that gastric irritation played a part in the production of nausea and vomiting. These observations are in accord with those of Finland[1] who pointed out ". . . . local gastric irritation may be an important contributing factor in the nausea and vomiting, irrespective of any possible central effect of the drug." Haviland and Blake[2] made similar observations on vomitus of patients receiving parenteral sulfapyridine. The findings in Case 2

suggest that the concentration of sulfapyridine in the stomach contents is many times higher after oral sulfapyridine than after intravenous sodium sulfapyridine alone. Nevertheless, the sulfapyridine blood levels are higher and the clinical response more dramatic in the latter. It appears, therefore, that there is less likelihood of nausea and vomiting after sodium sulfapyridine intravenously than after oral sulfapyridine. The danger of other toxic reactions probably is no greater, and the response to treatment more immediate and certain.

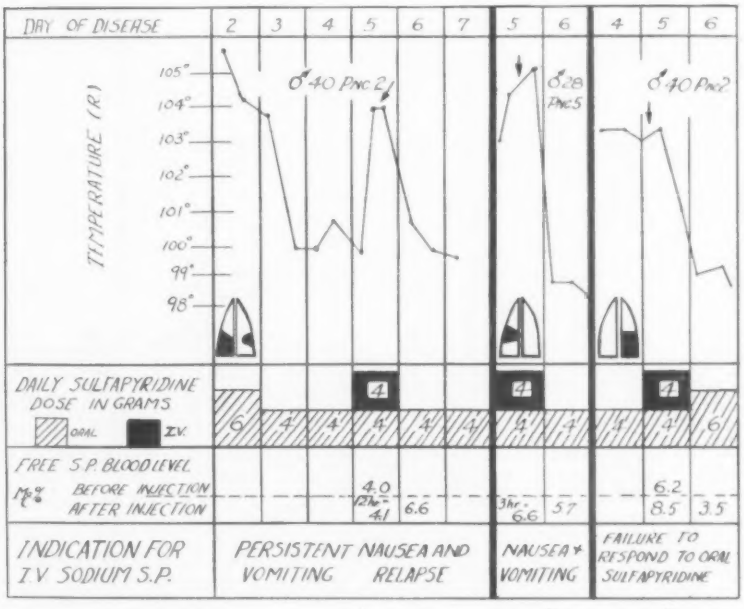
DAY OF DISEASE
2 3 4 5 6 7 5 6 4 5 6
TEMPERATURE (R)
105° 104° 103° 102° 101° 100° 99° 98°
♂ 40 Pnc 2
♂ 28 Pnc 5
♂ 40 Pnc 2
DAILY SULFAPYRIDINE DOSE IN GRAMS
ORAL I.V.
4 4 4
6 4 4 4 4 4 4 4 4 4 6
FREE S.P. BLOOD LEVEL
Mg% BEFORE INJECTION AFTER INJECTION
4.0 12hr. 4.1 6.6
3hr. 6.6 5.7
6.2 8.5 3.5
INDICATION FOR I.V. SODIUM S.P.
PERSISTENT NAUSEA AND VOMITING RELAPSE
NAUSEA + VOMITING
FAILURE TO RESPOND TO ORAL SULFAPYRIDINE
A B C

CHART 2.

Results (Table 1). Patients who were in coma or delirium when first examined were usually unable to take sulfapyridine orally. In such patients the bacteriologic diagnosis often could not be made in less than 12 hours and for this reason serotherapy could not be considered. There were 24 patients who were comatose or delirious at the time of admission. All appeared moribund. Intravenous sodium sulfapyridine was given in each instance, and 5 recovered.

The following is a summary of an illustrative case: H. R. (Chart 1, *A*), male, aged 38 years, was admitted to the hospital in a semicomatose state. He was able to take only the initial dose of sulfapyridine orally. He had an involvement of two lobes and a bacteremia. He also had an impending uremia and acidosis as shown by the blood chemistry (non-protein nitrogen 90 mg., creatinine 5.1 mg., CO_2

36 vol. %). Nausea and vomiting were persistent. Oliguria was present and became marked in 24 hours. Subsequently the blood non-protein nitrogen rose to 134 mg. White blood count on admission was 4000; 3 days later it had risen to 18,000. Intravenous sodium sulfapyridine together with sufficient glucose and fluid was given every 12 hours for 4 days. The patient became rational, coöperative and recovered from his pneumonia. The volume output of urine returned to normal, but the specific gravity remained low. The uremic state responded slowly. It was felt the nitrogen retention was the result of a previous nephritis, of which he gave a history, plus the superimposed pneumococcus infection, rather than a toxic manifestation of sulfapyridine.

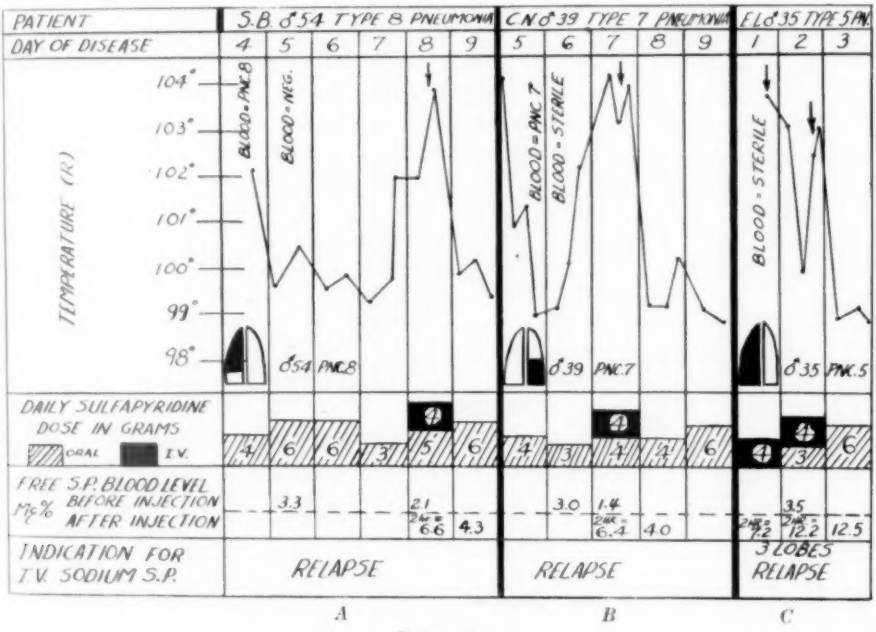

CHART 3.

Bacteremia was present in 37 of the 80 patients; 17 died, a mortality of 46%. In view of the type of cases that are often admitted to this hospital and that comprised this group, we feel this has some significance. Treatment was almost always delayed until after the fourth day of the disease.

In 4 patients showing a good initial response to oral sulfapyridine there occurred a recrudescence of the clinical signs and symptoms, indicating a reactivation or spread of their infection. Two of these patients had bacteremia. This occurred in the presence of inadequate blood levels (less than 5 mg. per 100 cc.) and before active

immunity had developed. In each instance intravenous administration of the sodium sulfapyridine brought about a favorable clinical response (see Charts 2*A*, 3*A*, *B*, *C*).

In 13 patients adequate oral dosage of sulfapyridine failed to bring about a decline in temperature and pulse within 24 hours. In some cases this was in spite of the fact the blood level was 5 mg. per 100 cc. or more. However, in all but 1 case prompt recovery followed the intravenous administration of sodium sulfapyridine.

Of the 75 patients treated with intravenous sodium sulfapyridine supplementary to oral sulfapyridine, 22 died (Tables 1 and 3). Fifteen died within 24 hours after admission to the hospital; 7 survived from 1 to 10 days (Table 3). Of these, 4 received serum

TABLE 3.—ANALYSIS OF DEATHS.

Case No.	Death.	Day of ill.	Age decade.	Etiology.	No. of injections.	I.V. S.P.	Oral S.P.	S.P. blood level.	Findings on first examination.
1	4 hrs.	5	6	Unc.	1	4.0	0	0	2 lobes; coma
2	4 hrs.	5	6	Pnc.	1	4.0	0	0	Meningitis
3	6 hrs.	5	5	II*	1	4.0	Yes	12.5	Pul. edema; semicoma
4	6 hrs.	2	3	Hemo-* Strep.	1	4.0	Yes	0	Benzol poisoning; aplastic anemia; semicoma
5	6 hrs.	7	6	II*	1	4.0	0	7.7	Coma; pul. edema
6	6 hrs.	5	6	II*	1	4.0	Yes	6.4	Pul. edema; 3 lobes
7	8 hrs.	4	6	VIII*	1	4.0	Yes	5.4	Semicoma; alcoholism
8	12 hrs.	5	6	I	1	4.0	Yes	8.3	Stuporous
9	12 hrs.	5	6	V*	1	4.0	Yes	0	Pul. edema; 2 lobes; arteriosclerosis
10	12 hrs.	5	6	II*	1	4.0	Yes	0	Coma; 3 lobes; pul. edema
11	12 hrs.	5	5	XXXIII*	1	4.0	Yes	0	Semicoma; 3 lobes; pul. edema
12	18 hrs.	2	3	B. Fried.*	1	4.0	Yes	5.7	
13	24 hrs.	7	6	Unc.	1	4.0	Yes	7.1	Coma; 3 lobes
14	24 hrs.	7	3	Pnc.	2	8.0	Yes	0	Broncho-pleural fistula; bronchiectasis; empyema; semicoma; tuberculosis
15	24 hrs.	7	3	II*†	2	8.0	Yes	9.2	Coma; 2 lobes
16	30 hrs.	4	1	Hemo-* Strep.	2	3.0	Yes	25.0	Empyema; semicoma
17	30 hrs.	5	3	XXVIII*†	2	8.0	Yes	10.0	Meningitis
18	2 days	5	5	III*†	1	4.0	Yes	5.0	Anaphylaxis (see text)
19	4 days	4	4	II*†	2	8.0	Yes	9.0	Oral sulfapyridine failure (see text)
20	5 days	3	6	I*	1	4.0	Yes	12.5	Thyrotoxicosis; aur. fib.; 2 lobes
21	10 days	6	6	II*	1	4.0	0	62.5	Nephritis; uremia; jaundice; lung abscesses
22	10 days	5	5	II*†	2	8.0	Yes	10.8	Delirium tremens; multiple lobes

* Bacteremia. † Serum was used in treatment.
Pnc. = pneumococcus no type. Unc. = no bacteriologic diagnosis made; I, II, etc. = pneumococcus type. S.P. = sulfapyridine.

therapy in addition to chemotherapy. One patient (Case 18) died from anaphylactic shock during the administration of serum. One patient (Case 17) who had pneumococcus meningitis and lobar pneumonia died 30 hours after entrance to the hospital. The 2 other patients who received serum (Cases 19 and 22) had Type II bacteremia and multiple lobe involvement. A patient (Case 21) in the sixth decade, who survived 10 days, had Type II pneumococcus pneumonia with bacteremia complicated by chronic nephritis with uremia, jaundice, and multiple lung abscesses. A child (Case 16),

8 years of age, developed pneumonia and empyema following scarlet fever. He was given intravenous sodium sulfapyridine before the bacteriologic diagnosis of hemolytic streptococcus was made. Bacteremia was present in 17 patients. Sixteen of the 22 fatal cases were admitted on the fifth day of their illness or later. The remaining 6 (Cases 4, 7, 12, 16, 19, 20) had an overwhelming infection on admission from which recovery could scarcely be hoped for. In all cases where blood concentrations of free sulfapyridine were determined, the levels (5.4–62.5 mg. per 100 cc.) were above those usually considered to be effective (5 mg. per 100 cc.).

Comment. Sodium sulfapyridine is a valuable addition to the armamentarium of the physician treating pneumonia and one that he should constantly keep in mind. It should not be used to replace oral sulfapyridine, the value of which has been so amply recorded during the last 2 years. However, there are times when parenteral administration is desirable and it is then that the sodium salt is of value. Patients who are unable to have serum, or who are unable to retain the drug orally because of nausea and vomiting, or who are unable to coöperate because of coma or delirium, are candidates for sodium sulfapyridine intravenously. It was given upon admission and followed by oral sulfapyridine in many of our patients whose condition appeared serious enough to warrant its use. The value of a sufficiently high blood concentration of sulfapyridine should not be overlooked in the treatment of the seriously ill patient. The presence of preëxisting disease or a complication of pneumonia made us feel that an effective blood concentration of sulfapyridine was imperative for best results. Also, it should be pointed out that all but 1 of 13 patients who failed to respond to oral sulfapyridine and 4 patients who had experienced a relapse made a prompt favorable response after sodium sulfapyridine was given intravenously. The high incidence of death in this series is readily explained by the fact that only those cases with a grave prognosis were selected for treatment with intravenous sodium sulfapyridine.

It is true that accidents may follow the intravenous use of sodium sulfapyridine, but in our experience these may be avoided by careful preparation and administration of the solution.

We wish to emphasize the benefits that may be derived from the intravenous use of sodium sulfapyridine in patients seriously ill with pneumonia and stress the importance of its therapeutic use alone, or in conjunction with oral sulfapyridine.

Conclusions. 1. No severe toxic reactions were seen during or following 115 intravenous injections of sodium sulfapyridine.

2. Response to treatment is more immediate with intravenous sodium sulfapyridine than with oral sulfapyridine.

3. Repeated at 12-hour intervals a dose of 0.06 gm. per kilo maintains a level of from 6 to 15 mg. per 100 cc.

4. The concentration of sulfapyridine in the stomach contents

probably produces sufficient gastric irritation to play an important part in the production of nausea and vomiting.

5. Intravenous sodium sulfapyridine is a valuable agent in critical patients when an immediate effective blood level is desired.

6. Fear of reactions following the intravenous administration of sodium sulfapyridine seems unwarranted and should not limit its more general application.

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ACCURACY OF FLUOROSCOPY IN THE DETECTION OF PULMONARY TUBERCULOSIS.

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Fluoroscopy continues to be widely employed for the detection of pulmonary tuberculosis, despite recent developments in other low-cost methods of Roentgen ray examination. The obvious disadvantage of fluoroscopic examination is the absence of a permanent record that may be reviewed by others or used for comparison in serial examinations. Nevertheless, the inexpensiveness of the method has resulted in its extensive use in diagnostic practice as well as in group examinations.

Studies estimating the accuracy of fluoroscopy as compared with conventional celluloid film examination have given widely divergent results. Investigations made prior to the introduction of the Patterson "B" screen showed gross inaccuracy in the detection of minimal and moderately advanced tuberculosis.[2] A study made at this Institute in 1932 indicated that apical infiltrations extending below the clavicle were in most instances detected, but tuberculous infiltrations limited to the lung field above the clavicle were seldom recognizable by fluoroscopic examination.[6]

More recent experience with the improved Patterson "B" screen has indicated a higher degree of accuracy for fluoroscopic examination.[1,5,8] Although some recent comparative studies have included large numbers of subjects,[4,8] they have been confined to student and employee groups in which the prevalence of tuberculous abnormalities is small.

Fluoroscopic examination has been used at this Institute since 1933 as a routine procedure in the study of new patients and in the periodic reëxamination of contacts as a screen to select persons for film examination. It seemed desirable to determine the accuracy of the method as used in the routine practice of the clinic; and to ascertain as well the limits of its accuracy in the detection of smaller lesions sought in epidemiologic studies.

This study includes 1021 duplicate fluoroscopic and film examinations made from June, 1938, to May, 1940. It seemed expedient to limit film examination to contacts, because in a limited series this should provide a larger number of tuberculous abnormalities, and because a film record of these patients was desired for the purposes of other investigations. In addition, duplicate examinations were given other patients in whom the routine fluoroscopic study suggested the presence of abnormalities.

The examining physicians were classed for purposes of comparison in three groups: 1, those having special training in roentgenologic interpretation and long experience in fluoroscopy; 2, staff physicians having considerable experience in fluoroscopy, but with limited or no special training in roentgenologic interpretation; and 3, fellows and graduate students receiving short periods of training.

Effort was made to obtain an unequivocal report from the fluoroscoping physician. Indiscriminate "suspicion" of abnormalities was discouraged. Physicians were directed to classify abnormalities as "definite," "probable" (suspected), or "possible" (slightly suspected).

Detection of Active Parenchymal Tuberculosis. Forty-eight of the 1021 patients had easily recognizable gross pleural abnormalities or non-tuberculous pulmonary or mediastinal diseases which made them unsuitable for the purpose of the present study. This group, which has been excluded from further consideration, was comprised of pleural effusion (15 patients), atypical pneumonia (14 patients), pulmonary abscess (4 patients), aneurysm (2 patients), residual lipiodol (2 patients), pneumatocele (2 patients), sarcoidosis (2 patients), silicosis (2 patients) and single instances of bronchiectasis, bronchogenic carcinoma, lymphoblastoma, pleural calcification, and substernal thyroid gland enlargement.

The remaining 973 patients have been classified into three groups, according to whether the presence of significant pulmonary infiltrations was considered by the fluoroscopist to be definite, probable, or unlikely (Table 1). Infiltrations were thought to be absent or unlikely in 692 patients; in 668 instances (96.6%) this diagnosis was confirmed by film examination. The presence of a tuberculous infiltration was thought to be definite on fluoroscopic examination in 246 patients; in 237 instances (96.7%) this diagnosis was confirmed. In the other 35 patients infiltrations were thought probably to be present; film examination revealed definite lesions in 10 (28.6%).

TABLE 1.—DETECTION OF ACTIVE PARENCHYMAL TUBERCULOSIS BY FLUOROSCOPY.

Physician.	Experience.*	No. of duplicate examinations.	Excluded (non-tbc. lesions).	Lesion absent or improbable.		Lesion probable, fluoroscopy.	Lesion definite, film.	Lesion definite.	
				Fluoroscopy.	Film.			Fluoroscopy.	Film.
A	Group I	150	5	96	96	4	1	45	44
B		142	2	115	113	2	1	23	22
C	Group II	170	12	100	97	12	3	46	45
D		95	2	66	65	1	0	26	25
E		89	9	53	49	3	1	24	24
F		70	5	47	41	1	1	17	17
G	Group III	62	1	40	37	2	2	19	19
H		57	2	44	43	2	0	9	7
I		38	2	27	25	2	0	7	7
J		37	4	24	23	1	1	8	8
K		35	1	32	31	0	0	2	2
L		26	2	13	13	3	0	8	6
M		23	0	19	19	1	0	5	5
N		9	1	3	3	0	0	5	5
O		7	0	7	7	0	0	0	0
P		6	0	4	4	0	0	2	2
Q		3	0	1	1	0	0	2	2
R		2	0	1	1	1	0	0	0
Total	...	1021	48	692	668 (96.6%)	35	10 (28.6%)	246	237 (96.7%)

* Classification described on p 225.

It is evident that individual variations in accuracy occurred but were relatively slight. Experienced physicians of Group I were approximately 99% accurate in excluding tuberculosis, while physicians in Group II were 94.9% accurate, and the least experienced physicians of Group III were 97.3% accurate.

Reinfection Type Tuberculosis. Far-advanced tuberculosis was present in 116 patients (Table 2). All of these appeared to the fluoroscopist as definite infiltrations.

TABLE 2.—ACCURACY OF DETECTION OF REINFECTION-TYPE TUBERCULOSIS BY FLUOROSCOPY.

Extent.	Number found by film examination.	Fluoroscopic report.			
		Lesion definite.	Lesion probable.	Lesion possible.	Negative.
Far advanced	116	116	0	0	0
Moderately advanced	52	51	0	0	1
Minimal:					
a. Treatment advised	43	37	3	1	2
b. Observation advised	36	13	5	11	7
Apical pleuritis	40	10	0	5	25

Moderately advanced tuberculosis was present in 52 patients. In 51 instances the lesions were definite on fluoroscopic examination. One patient, reported as negative on fluoroscopic examination, was

given film examination a week later because of suggestive symptoms, and moderately advanced tuberculosis was found. Reëxamination by another fluoroscopist clearly revealed the lesion.

Minimal tuberculosis was present in 79 patients. These have been subdivided into two groups, the first comprising patients whose lesions were sufficiently marked to warrant reporting to the Board of Health and to require immediate treatment. The second group comprised patients with smaller infiltrations, usually confined to the lung field above the clavicles, of questionable clinical significance. Continued observation was the customary recommendation for patients with these small apical infiltrations. Minimal lesions requiring treatment were present in 43 patients. In 37 instances the infiltrations appeared definite to the fluoroscopist; in 3 instances the presence of an infiltration was suspected; in 1 instance possible infiltration was reported; and in 2 instances the fluoroscopist failed to detect the abnormality. Smaller minimal lesions, for which observation was advised, were present in 36 patients. In 13 instances the infiltrations appeared definite; in 5 instances the presence of a lesion was suspected; in 11 instances possible infiltration was described, and in 7 instances the fluoroscopic report was negative.

Projections of thickened pleura at the extreme apex, presumably representing obsolete tuberculous foci and considered to be merely of epidemiologic significance, were present in 40 patients. Only in 10 instances did these scars appear as definite lesions on fluoroscopic examination; in 5 instances possible lesions were described; and in the remaining 25 instances no abnormality was noted by the fluoroscopist.

Tracheobronchial Lymph Node Tuberculosis. Definite tracheobronchial lymph node enlargement, presumably due to caseous tuberculosis, was reported on fluoroscopic examination of 22 patients (Table 3). In 18 instances the same diagnosis was reported on film examination. Tracheobronchial lymph node enlargement was considered probable in 40 patients. Film examination showed definite enlargement in only 8 of these patients.

TABLE 3.—ACCURACY OF DETECTION OF TUBERCULOUS TRACHEOBRONCHIAL LYMPH NODE ENLARGEMENT BY FLUOROSCOPY.

Fluoroscopy: Lesion definite	22
Confirmed by film examination	18
Fluoroscopy: Lesion probable	40
Lesion definite on film examination	8

Three additional patients were found on film examination to have enlarged tuberculous tracheobronchial lymph nodes. In one instance possible enlargement was described by the fluoroscopist, and in two instances the fluoroscopic report was negative.

A total of 29 cases of tracheobronchial lymph node enlargement was found on film examination of the entire group. On fluoroscopic examination, as noted above, 18 had appeared definite and 8 prob-

able. Possible lymph node enlargement was described in 1 patient, and in 2 the fluoroscopic report was negative.

Calcified Primary Tuberculosis. Calcified foci in the lungs and tracheobronchial lymph nodes are identified in Roentgen ray films by their density, irregularity in outline, sharply defined margins and not infrequently by their position or site in the lung field. It is often necessary to take films in rotated positions or with over-exposed technique in order to make certain that the shadows are due to calcium deposition and not to blood-vessels. Since these lesions are not regarded as clinically significant, no attempt was made in the present study to determine their incidence accurately by rotation films. Fluoroscopy has the advantage of permitting the operator to rotate the patient and thus differentiate shadows of vessels from calcified foci. For this reason a density due to calcium may be seen on fluoroscopy but not recognized as such in the Roentgen ray film. On the other hand, since these lesions are so much less important than pulmonary infiltrations, fluoroscopists are unlikely to make as careful a search for their presence. These factors are presumably responsible for the divergent results obtained by fluoroscopic and film examination in the present study.

The presence of tracheobronchial lymph node calcification or of a calcified peripheral nodule was described as definite on fluoroscopic examination in 105 patients (Table 4). The same diagnosis was made on film examination in 82 instances. Probable calcified primary lesions were reported in 14 patients. Definite calcification was reported on film examination in 8 of these patients.

TABLE 4.—ACCURACY OF DETECTION OF CALCIFIED PRIMARY LESIONS BY FLUOROSCOPY.

Type of lesion.	Number diagnosed on film examination.	Fluoroscopic report.			
		Lesion definite.	Lesion probable.	Lesion possible.	Negative.
Peripheral nodule	50	28	2	0	20
Tracheobronchial node	64	35	3	1	25
Complex	29	19	3	0	7

In 105 patients a calcified primary lesion appeared definite on fluoroscopy; the lesion appeared definite on film examination in 82 instances.

In 14 patients a calcified primary lesion appeared probable on fluoroscopy; film examination showed a definite lesion in 8 of these patients.

A total of 143 calcified primary lesions was reported on film examination. These lesions appeared definite to the fluoroscopist in 82 instances, probable in 8 instances, and possible in 1 instance. In 52 instances no calcification was reported by the fluoroscopist. Table 4 indicates that the discrepancies in diagnosis between fluoroscopic and film examination were equally marked in the case of peripheral nodules and in the case of tracheobronchial calcifications. More consistent results were obtained when both components of the primary complex were present.

Obesity. It is generally believed that fluoroscopy is unsatisfactory for the examination of obese adults. In the present study, the fluoroscopist noted in 31 instances that examination was not entirely satisfactory because of marked obesity. Mediastinal lymph node enlargement due to lymphoblastoma was detected in 1 of these patients. The fluoroscopist reported tuberculous infiltration in 2 patients; in 1 patient, film examination failed to confirm the diagnosis, while in the other, it showed minimal tuberculosis. In the remaining 28 patients fluoroscopic examination was reported as negative for tuberculosis. This diagnosis was confirmed in 27 instances. The single lesion missed was a small minimal apical infiltration of questionable clinical significance.

This series, although small, suggests that fluoroscopic examination even in the obese will detect tuberculous infiltrations of immediate clinical significance.

Fluoroscopy in Children. One hundred and twenty-nine of the duplicate examinations reported in this series were made in children less than 13 years of age. The majority of these were aged 4 to 12 years, since fluoroscopic examination was rarely attempted in infants. Advanced tuberculosis with cavity was found in a negro child of 4 years. A pleural effusion was detected in 1 white child. Apical tuberculosis of minimal extent was found in a negro girl of 12 years. Infiltration was suspected in a 5-year-old negro child; film examination demonstrated miliary tuberculosis.

Fluoroscopic examination was reported negative in 74 children; film examination confirmed this diagnosis in every instance. Active primary type tuberculosis was considered definite on fluoroscopic examination of 23 children. In 14 instances the same diagnosis was made on film examination, and in 2 instances a diagnosis of suspected tuberculosis was made. In 28 children the presence of active primary type tuberculosis was considered probable on fluoroscopic examination. In only 3 of these children was a definite diagnosis of tuberculosis made on film examination. It is noteworthy that in 12 children the same diagnosis of probable tuberculous tracheobronchial lymph node was made on fluoroscopic and film examination.

Calcified primary lesions appeared probable or definite on fluoroscopy in 10 children. Calcification appeared definite on film examination in 8 of these children. Nine other children in whom calcification was not suspected on fluoroscopic examination were diagnosed as having calcified primary lesions on film examination.

Individual Variations in Accuracy. Fluoroscopic examinations made by 18 physicians are included in this study. Individual variations in accuracy were not marked (Table 1). Nevertheless, it appears significant that 2 physicians were responsible for the 4 instances in which infiltrations of immediate clinical significance were missed by fluoroscopic examination. One of these physicians

had had considerable experience in fluoroscopy and was receiving special training in chest roentgenology. The other physician had had relatively little roentgenological experience.

Dark adaptation studies were made to determine whether the individual variations might be due to poor dark adaptation caused by vitamin A deficiency or to some interference with the scotoptic mechanism in the eye. Twelve staff physicians were examined with the Hecht dark adaptometer, through the kindness of Dr. Robb McDonald, of the Department of Ophthalmology in the School of Medicine of the University of Pennsylvania. No significant abnormality was found in any of the physicians.

Further study was directed toward determining the relative visual acuity of the various physicians as measured by ability to define under the fluoroscope the orientation of small slits made in discs after intervals of dark adaptation of 2, 5 and 8 minutes. Although a method satisfactory for quantitative comparison was not developed, preliminary studies confirmed the finding of Chantraine and Cramer[8] that considerable variation exists in the relative visual acuity of individual physicians as tested by this method.

It seems reasonable to conclude that failure to wait for adequate dark adaptation was responsible for the occasional gross inaccuracies rather than lack of training or limitations of the fluoroscope. Smaller supraclavicular lesions, on the other hand, were frequently overlooked by physicians who had not had special training in film interpretation. Such small lesions would probably have been disregarded by these men on films as well as on fluoroscopic examination. In a number of patients, however, small lesions of this type are not recognized even on careful examination by experienced physicians; these instances indicate that fluoroscopic examination cannot be relied upon for the detection of the earliest lesions of pulmonary tuberculosis. This finding is in accord with Hedvall's conclusion.[7]

Discussion. Duplicate fluoroscopic and film examinations given 1021 patients who had history of respiratory symptoms or history of exposure to tuberculosis, indicate that in clinical practice fluoroscopy provides an accurate method for the detection of pulmonary tuberculosis. Abnormalities appeared definite or probable to the fluoroscopist in 329 of these patients; of the remaining 692 patients in whom no definite abnormality was reported on fluoroscopic examination, only 4 (0.6%) had tuberculous lesions of immediate clinical significance. Fluoroscopy was less satisfactory in the detection of smaller apical infiltrations that would be merely observed or disregarded by the clinician, although of great interest to the epidemiologist. In 18 instances in this series, fluoroscopic examination failed to detect these small but not necessarily obsolete minimal apical lesions which represent, as Hedvall[7] has shown, the earliest roentgenologic evidence of pulmonary tuberculosis. As far as the use of

fluoroscopy in clinical practice is concerned, however, it is only fair to state that lesions of the type described by Hedvall are demonstrable only on films made with superior technique, and are at present overlooked by the majority of roentgenologists and disregarded by most clinicians.

Stiehm[8] has reported several instances in which significant infiltrations detected by fluoroscopic examination were so hidden by superimposed bony structures that they were not detected on single film examination. Although no instance of this occurred in the present series, 2 such cases have recently been encountered in a study of the development of tuberculosis in nursing students. Infiltrations have been found on fluoroscopic examination of 2 students in whose films, taken at another institution, no certain abnormality could be distinguished.

The accuracy with which tuberculous infiltrations can be detected in children is even greater, as might be expected from their easier radiability and the lesser prevalence of small supraclavicular lesions in children. Duplicate examinations given 125 children less than 13 years of age revealed no instance in which a tuberculous infiltration was overlooked on fluoroscopic examination.

Tuberculous tracheobronchial lymph node enlargement, definite on film examination, was detected in all but 2 instances by fluoroscopy. As a rule, when lymph node enlargement was definite on one method of examination, it appeared definite on the other; when probable on one method of examination, it appeared probable on the other. It is questionable whether film or fluoroscopic examination is the more authoritative in the diagnosis of tuberculous lymph node enlargement.

It is similarly questionable which is the more accurate method for the diagnosis of calcified primary lesions. In a considerable number of patients in this study calcification appeared definite on fluoroscopy, while flat film examination showed no abnormality that would warrant a definite diagnosis of calcified tuberculosis. An even larger proportion of patients diagnosed as having a calcified primary lesion on flat film examination was considered negative on fluoroscopy. The discrepancies were so great that diagnoses of calcified primary tuberculosis made on fluoroscopic examination alone or on flat film examination alone must be regarded with a measure of skepticism.

Conclusions. 1. Fluoroscopic examination by physicians with limited training and experience in fluoroscopy should detect in diagnostic practice or in mass surveys almost all tuberculous infiltrations of immediate clinical significance. In the present series of approximately 1000 duplicate examinations, in only 4 instances were significant lesions of this type not recognized. Results satisfactory for clinical purposes were obtained even in obese patients.

2. Smaller tuberculous lesions of questionable clinical significance,

but of considerable importance in epidemiologic investigations, were frequently overlooked by physicians without special training in roentgenologic interpretation. In most instances physicians who had special training and experience were able to detect even these minute lesions.

3. Individual variations in accuracy among the group of 18 physicians studied were not correlated with vitamin A deficiency or local changes that might cause poor dark adaptation. It seemed probable that failure to wait for adequate dark adaptation was the chief factor responsible for poor results.

4. An especially high degree of accuracy was observed in the fluoroscopic examination of children.

5. The results of fluoroscopic and film examination in the diagnosis of tuberculous tracheobronchial lymph node enlargement corresponded closely.

6. Rather inconsistent results were given by fluoroscopy and by flat film examination in the diagnosis of calcified primary lesions. Which of the methods is the more accurate is not proven.

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SPONDYLARTHRITIS ANKYLOPOIETICA.

A Review and Report of Twenty Cases.

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Although spondylarthritis ankylopoietica has long been recognized as a clinical and pathologic entity, it is our belief that there still exists some confusion about it among internists in general. It seems useful, therefore, to report the 20 cases studied by us and to review more extensively than has been done in the American medical literature the development of the present concept of the disease. The European literature, particularly the German, has from time to time contained excellent discussions of the subject, notably by Simmonds,[71] Fraenkel,[19a,b] Proebster,[58] Krebs,[38a] and Ehrlich.[15c] In this country important papers by the late Dr. Joseph L. Miller[53a,b] should be mentioned.

Spondylarthritis ankylopoietica is a chronic, progressive, probably infectious disease of the vertebral column and adjacent structures, occurring chiefly in young adult males, and characterized clinically by pain and stiffness in the back, with or without involvement of the hip and shoulder joints. There is early ankylosis of the small posterior intervertebral articulations and of the sacro-iliac joints, along with marked atrophy of the vertebral bodies. The costochondral joints may become ankylosed. Calcification of the longitudinal ligaments of the spine may take place producing the so-called "bamboo spine." The disease is subject to exacerbation and remission and the changes described in the spine may progress in the absence of pain.

Material. Among the 2395 patients registered at the Desert Sanatorium prior to January 1, 1936, there were diagnosed 228 cases of atrophic arthritis, 115 cases of hypertrophic arthritis, and 42 of "spondylitis." Among the case records of patients suffering from "spondylitis," with or without other joint disease, roentgenograms were available for study in 36 instances, and we were able to make a diagnosis of spondylarthritis ankylopoietica in 20 of these. The records of those patients not actually seen by the present authors were carefully reviewed. The material from the 20 cases of spondylarthritis ankylopoietica has been collected in Table 1. References will be made later in this paper to an unpublished statistical study of the complete records of 201 cases of atrophic arthritis and 95 cases of hypertrophic arthritis.

Historical.—Previous to 1893, cases of primary rigidity of the spine had excited little special interest and were classified as "spondylitis deformans." In that year Bechterew[5a] published a paper in which he described what he believed was a new neurologic disease, characterized by stiffness of all or part of the spine, a kyphosis involving chiefly the upper thoracic spine, paresis of the muscles of the neck, back, and extremities, atrophy of the shoulder girdle and of the back muscles, reduced skin sensitivity over the areas supplied by the cervical and other spinal nerves, and finally prominent symptoms of root irritation. Bechterew described in detail the cases of 2 female patients, both in the sixth decade of life, with symptoms of 2 and 5 years' duration. A third case was that of a young male patient 39 years old, who had suffered from the disease for 10 years. Bechterew stated that the man was suffering from a much more severe illness than were the women. In the same paper Bechterew included brief notes on 2 patients seen by him some years previously. Both of these were elderly males. He postulated that a diffuse ankylosing process in the spine was associated with an inflammation of the epidural sheaths, and that heredity and trauma were the chief factors in initiating this condition. In 1897 Bechterew[5b] reported another case which he believed belonged in the same group.

In the same year (1897) Strümpell[77] described the case of a 39-year-old male who during the previous 4 years had gradually developed ankylosis of the spine and of the hip joints. In this case there was no question of a senile kyphosis. Strümpell also included notes on 2 other similar patients previously seen by him. Both of these were young adult males. The following year, 1898, Pierre Marie,[48] presented in detail 3 cases of rigid spine occurring in males all of whom placed the onset of their illness in the fourth

TABLE 1.—SUMMARY OF DATA IN 20 CASES OF SPONDYLARTHRITIS ANKYLOPOIETICA. ARRANGED ACCORDING TO DURATION.

					Roentgenographic findings.										Clinical findings and history.												
Patient.	Case number.	Age of onset.	Duration in years.	Period of observation.	Posterior articulations.	Calcification of longitudinal ligaments.	Narrowing of intervertebral spaces.	Sacro-iliac joints.	Ischia.	Pubes.	Iliac crests.	Hip joints.	Shoulder joints.	Peripheral joints.	Sedimentation rate.	W.B.C. in thous.	Fever.	Hemoglobin, °C.	Serum calcium.	Serum phosphorus.	Urine.	Conditions associated with onset.	Chronic diseases.	Acute episodes.	Rheumatic fever.	Scarlet fever.	Family history of joint disease.
K.J.	484	23	3	3 mos.	+	–	–	4+	–	–	–	–	–	..	+	9–10	+	96	....		1–2 W.B.C.	.....	Splenomegaly Eosinophilia Lymphadenopathy	....	..	5 yrs.	
R.Q.	3060	21	3½	18 mos.	2+	–	2+	4+	+	+	2+	–	..	..	+	9.4	–	105	....		Occ. W.B.C.	Sacro-iliac strain	Mitral valve	Iritis	10 yrs.		
R.W.	723	26	4	5 yrs.	3+	–	±	4+	–	+	–	–	..	–	+	9.9	±	103	10.1/3.5		Occ. W.B.C.	.....	Pulmonary tube.				
E.H.	888	24	4	7 yrs.	4+	3+	2+	4+	+	2+	–	±	+	–	+	9.0	±	100	....		Occ. W.B.C.	.....	Pericarditis Pneumonitis	Iritis			
R.C.R.	297	23	4½	1 yr.	4+	3+	+	4+	2+	2+	–	2+	+	–	+	10.8	–	80	10.6/		–	Paratonsillar abscess	Otitis				
J.G.	236	24	5	3 mos.	4+	3+	–	4+	3+	3+	3+	3+	2+	–	+	8.4	–	90	....		–	.....	.....	Iritis			
W.MC.	332	18	6	6 yrs.	4+	4+	3+	4+	4+	2+	4+	2+	–	..	+	6.8	±	92	9.5/3.9		Occ. W.B.C.	Polyarthritis or rheumatic fever	Acne vulgaris				
M.M.	2803	27	7	3 yrs.	4+	4+	–	4+	2+	3+	4+	2+	–	..	+	11.8	+	88	....		Occ. W.B.C.	.....	Ischiorectal abscess	Iritis Pneumonia			
O.R.	1042	27	7½	1 wk.	4+	3+	+	4+	4+	–	2+	2+	–	..	+	10.6	+	65	....		10–15 W.B.C.	.....	Pulmonary tube.	.....	..	..	+
J.C.	417	27	8	4 mos.	4+	–	+	+	–	+	3+	–	+	2+	+	9.0	+	38	....		5–10 W.B.C.	Acute G.C.					
W.J.	719	21	8	9 mos.	4+	–	±	4+	+	+	+	–	–	–	+	10.6	+	81	....		2–3 W.B.C.	Trauma to spine	Chronic bronchitis	Thyrotoxicosis			
W.R.S.	4	26	11	9 mos.	4+	4+	+	..	..	..	..	..	..	..	+	14.2	+	80	....		Occ. R.B.C. Bacillurea	.....	Pulmonary tube. fatal				
B.W.	2079	21	11	4 yrs.	4+	2+	–	..	..	..	..	..	..	–	+	14.8	+	93	....		3–30 R.B.C.	.....	.....	Spontaneous pneumothorax			
W.K.	665	24	11	1 wk.	2+	+	–	3+	–	–	–	2+	..	2+													
M.O.	575	36	13	10 mos.	4+	4+	3+	4+	2+	–	2+	–	–	..	+	13.7	±	83	....		Occ. W.B.C.	Fistula-in-ano	Coronary disease	....	..	..	+
E.G.	2177	20	15?	10 mos.	4+	4+	2+	4+	2+	–	2+	2+	2+	..	+	11.3	±	105	....		10–20 W.B.C.	War exposure					
M.K.	2749	18	14	1 day	4+	4+	3+	4+	4+	–	–	3+	..	..	+	8.2	..	100	9.6/		–						
H.M.	554	40	15	2 yrs.	4+	4+	+	4+	2+	2+	–	–	–	2+	+	13.4	+	77	9.8/4.3		Occ. W.B.C.	.....	Pulmonary tube.	Renal colic			
W.B.	86	33	20	5 mos.	4+	4+	3+	4+	4+	4+	4+	+	–	..	+	8.8	..	80	....		1–3 W.B.C.	Typhoid	.....	Iritis Pericarditis	..	..	+
R.C.	940	26	24	3 mos.	4+	4+	+	4+	4+	4+	4+	2+	–	..	+	14.2	–	91	....		Occ. W.B.C.	Chronic G.C. Scarlet fever	.....	Pneumonia with empyema	18 yrs.	26 yrs.	

decade of life. He also included in this paper notes on 2 other cases of his own and on Strümpell's case. He felt that this group of 6 cases represented a clinical entity characterized by complete fusion of the dorsal and lumbar spine, associated with a more or less pronounced ankylosis of the shoulder and hip joints, and without involvement of the small joints of the extremities. Marie[49] asserted that these cases were distinct from the one which he and Astié had reported in 1897, the latter being similar to the cases described by Bechterew. As none of his patients had come to autopsy Marie described in detail and illustrated in his text a skeleton from Dupuytren's collection, which he felt represented what would be found in a case of "Spondylose Rhizomélique." This skeleton presented the picture that we now know is characteristic of spondylarthritis ankylopoietica. Such spines had been observed and described before (Gurlt,[29] Braun[7]), but for the most part were not clearly differentiated from those with "Spondylitis Deformans" (hypertrophic arthritis of the spine). According to Buckley,[9] typical skeletons had been described by Connor in 1700 and by Hilton Fagge in 1877. V. Leyden[45] clearly described the two pathologic types, but classified them both as "Spondylitis Deformans." Marsh[51] in 1895 gave a particularly clear description of such a spine, pointing out the calcification of the longitudinal ligaments, and the absence of any decrease in the intervertebral spaces. Marie, however, was the first to correlate the clinical picture of spondylarthritis ankylopoietica and the anatomic changes present in the spine.

In 1899 Bechterew[5c] reviewed his earlier cases and reported 2 of "Strümpell's Disease" in males. Bechterew again asserted his belief that he had described a distinct clinical entity.[5d] He emphasized the occurrence of kyphosis in his disease as opposed to an abnormal straightness of the spine in the cases reported by Strümpell and Marie. He[5d,e] reported the findings at autopsy on one of his male patients who had died of pneumonia. There was a dorsal kyphosis. Osteophytes were noted on the thoracic vertebræ, along with complete or partial fusion of most of the dorsal vertebræ. The intervertebral spaces were much reduced, especially in the regions where the vertebræ had grown together. The above description makes it likely that he was dealing with an advanced case of hypertrophic arthritis of the spine with kyphosis. Certainly here was no new neurologic disease.

In the same year Marie and Léri[50] presented the autopsy findings in the case of a patient who had suffered from "Spondylose Rhizomélique." The striking feature was the great involvement of the posterior articulations of the spine, most of which were completely ankylosed. There was no calcification of the anterior or posterior common ligaments.

Articles appeared early in the American literature. Dana[13] presented a thorough discussion of it. Goldwaith[26] recognized two forms of arthritis of the spine, osteo-arthritis and rheumatoid arthritis, but he seems to have fallen into the error, still common, of confusing advanced cases of spondylarthritis ankylopoietica with hypertrophic arthritis of the spine. Elliot[16] in 1905 pleaded for more pathologic studies of these cases and less speculation. He reported the autopsy findings in 1 case.

Between 1898 and 1904 innumerable papers were published on the subject. They consisted chiefly of case reports accompanied by conjectures about the etiology and pathology of rigid spine (Schultze,[67] Popoff,[56] Schataloff,[63] Sänger,[61] Jacobi and Beckman,[32] Hoffman,[31] Damsch,[12] Bregman,[8] Müller,[54] Galliard,[22] Kudrjaschoff,[40] Anschütz,[1] and Magnus-Levy[47]). With neither pathologic nor roentgenographic evidence to support their views these authors did little to clarify the situation.

In 1899 Valentini[83] published an important paper describing 2 patients who had had symptoms for 10 years. In 1 case roentgenograms had been made and showed what is commonly termed "bamboo spine." In the same year Méry[52] reported a case of rigid spine in a man 38 years old. Symptoms

had been present for only 3 years. The roentgenograms made in this case showed no evidence of "bamboo spine." Méry observed, however, that there was no narrowing of the intervertebral spaces.

In 1900 Heiligenthal[30b] assembled the records of most of the cases reported up to that time and summarized them in tabular form with a full bibliography. He attempted, not altogether successfully, to separate the cases into two groups, those resembling the cases reported by Strümpell and Marie, and those characteristic of "Bechterew's Disease." About this time Senator[70] and Schlesinger[65] published reviews on the pathology of ankylosing processes involving the spine. The latter failed to note, however, that in characteristic cases of one type the involvement of the costovertebral articulations was of a degree never seen in "Spondylitis Deformans." Glaser[24] laid particular emphasis on the occurrence of the disease in young adults of the male sex. Pribram[57] stated that "generalized ankylosis of the vertebral column" had a definite pathology as described by Marie. As for Bechterew's cases he believed that the lesions were essentially local. Reuter[59] and Sivèn[72] were of the same opinion. The latter reported 4 cases in which roentgenographic studies had been made.

In 1904 two papers on this subject appeared in the same issue of the same journal. The first by Simmonds,[71] presented a particularly lucid description of the pathologic anatomy of spondylarthritis ankylopoietica and spondylitis deformans. Simmonds stated that he believed spondylitis deformans was a condition that appeared secondary to damage of the intervertebral disks. In his 2 cases of "ankylosing spondylitis" all of the intervertebral and costovertebral articulations were ankylosed. The intervertebral disks appeared somewhat thinned but were completely intact. The surfaces about the joints were smooth excepting for an isolated exostosis present on one lumbar vertebra. The posterior articular processes were ankylosed without exostosis formation. There was extensive ossification of the ligaments including the ligamenta flava. The other article, by Fraenkel,[19a] confirmed the findings of Simmonds. Fraenkel emphasized that bony ankylosis of the costovertebral joints was rare in "Spondylitis Deformans," and never generalized. He drew the material for his discussion of "ankylosing arthritis of the vertebral column" from 4 cases which had come to autopsy. Like Simmonds, he stressed the constant finding of bony union between the posterior articular processes, and emphasized the fact that the vertebral bodies and intervertebral disks were intact. Neither he nor Simmonds was able to distinguish between a Bechterew and a Strümpell-Marie type. With these two papers the anatomic changes in the spine in spondylarthritis ankylopoietica were stated in unmistakable terms. The cases reported by these authors had been followed clinically and studied at the autopsy table. No longer could the objection be raised that findings on isolated skeletons without clinical histories were being ascribed to these cases.

In 1906 Schlayer[64] presented the first good discussion of the roentgenographic findings. He demonstrated, for the first time on a roentgenogram, ankylosis of the posterior vertebral articulations. This he was able to do in 11 out of 12 cases. He was thus able to confirm the findings of Fraenkel and Simmonds. Furthermore, he was able to explain the confusion that had attended attempts to classify cases as Bechterew or Strümpell-Marie. He showed conclusively that the cases which were clinically Strümpell-Marie were true "ankylosing spondylo-arthriti. " while cases that were clinically Bechterew might either be "ankylosing spondylo-arthritis" or "Spondylitis Deformans" with dorsal kyphosis. In 1907 Fraenkel[19b] reviewed the subject, adding reports on specimens from 2 more cases and using the name "Spondylarthritis Ankylopoetica."

We believe with Max Lange[42] that it is less confusing if we forget the names of Bechterew, Pierre Marie and Strümpell when considering cases of

rigid spine, and think in terms of spondylarthritis as opposed to other diseases of the spine such as infectious spondylitis and hypertrophic osteoarthrosis (spondylitis deformans and hypertrophic arthritis). Certainly the evidence points to the fact that Bechterew was not describing a pathological entity.

Pathology. In recent years important features of the pathologic anatomy of spondylarthritis ankylopoietica have been added to our knowledge of the disease, notably the changes which occur in and

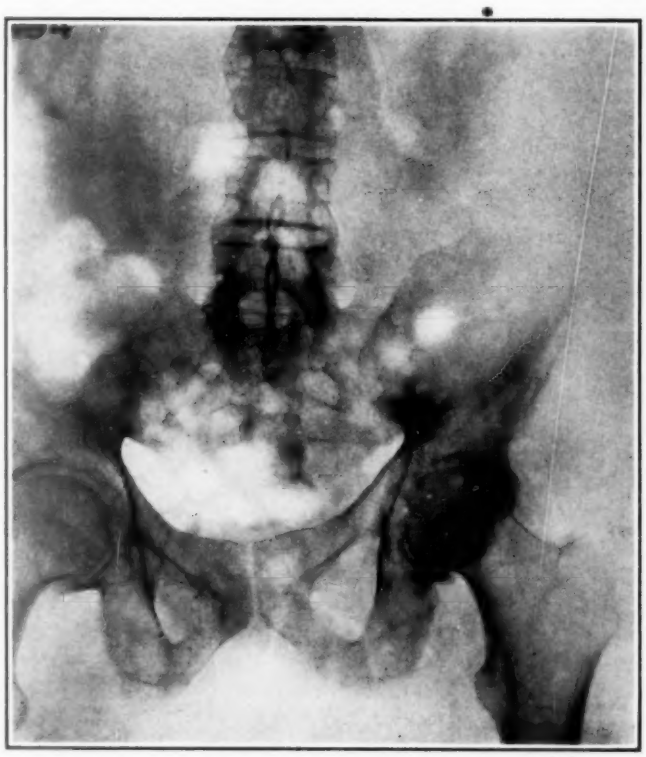

FIG. 1.—Lumbosacral spine and pelvis in Case O.R. showing marked bone atrophy, complete fusion of the posterior intervertebral articulations, incomplete calcification of the longitudinal ligaments, intact intervertebral disks, complete fusion of the sacro-iliac joints, exostoses on the ischia, and changes in and about the hip joints.

about the pelvic girdle. Nothing, however, has been added to the observations of Simmonds and Fraenkel on the gross changes as they affect the spine itself.

Although these and other authors had referred to involvement of the sacro-iliac joints, Krebs and Vontz[38b,39] (1934) seem to have been the first to recognize that this constitutes an essential part of the disease. Krebs[38b] believes that the finding of changes in the sacro-iliac joint is the earliest and most characteristic sign. This view is

consistent with our finding of well-developed changes in the sacro-iliac joints at a time when involvement of the posterior vertebral articulations was slight (Cases K. J., R. G., and W. K.). In all of Wolff's 15 cases there was a more or less pronounced calcification of the sacro-iliac joints. The first demonstrable abnormality, according to Vontz,[84] is a spotty loss of contour of the joint surfaces and narrowing of the joint space.

Krebs and Vontz described the occurrence of patchy areas of increased density in the ischia and pubes with roughening of the periosteum and exostosis formation. Krebs interpreted this as evidence for a diseased state of the periosteum and adjacent fibrous tissue. He also described "ulcerous" defects at the symphysis pubis and bridging of the symphysis. Such changes were a prominent feature in many of our cases, and in one (R. Q.) they were observed fairly early in the course of the disease.

In the spine itself involvement of the small posterior intervertebral articulations is of primary interest. Guntz[28] was able to study histologic preparations representing various stages of this process. In the early stage there is inflammation of the joint surfaces with exudation, invasion of the cartilage by round cells, and production of connective tissue. With further progress of the disease only islands of cartilage remain, and finally complete bony ankylosis takes place. This process, although it does not involve all of these joints simultaneously, is never an isolated affair limited to one or two joints. The same is true of the destruction and eventual ankylosis of the costovertebral articulations. Exostosis formation about these joints is rare.

The essential change in the bodies of the vertebræ is a high-grade atrophy which appears early in the course of the disease (Schmorl[66]). There is no tendency for the vertebræ to collapse. The intervertebral disks are remarkably immune from active involvement throughout most of the course of the disease, and the intervertebral spaces remain intact in the presence of a generalized involvement of all of the other vertebral articular surfaces. In preparations from individuals who had had the disease for many years, however, Schmorl found some tendency to narrowing of the intervertebral spaces and observed the presence of spongy bone in the intervertebral disks.

Fraenkel and many others believe that calcification of the longitudinal ligaments of the spine occurs secondarily to ankylosis of the small intervertebral articulations. Schmorl[66] is not so certain that this is the case, and Ehrlich[15a] has reported cases where there was a marked "bamboo spine" without demonstrable involvement of the small joints. Oppenheimer,[55] however, states that ossification of the ligamenta flava occurs about the time that ankylosis of the small joints becomes bony, and that ossification of all of the longitudinal ligaments never occurs until ankylosis of the small joints in the affected region is complete. In our series of cases there is no

instance in which there was Roentgen ray evidence of calcification of the longitudinal ligaments in the absence of demonstrable involvement of the small articulations. In several instances (K. J., R. Q., R. W., J. C., and W. J.) the reverse was observed. Vontz[84] believes that ossification of the longitudinal ligaments begins in the region of the twelfth dorsal vertebra.

FIG. 2.—Lateral view of cervical spine in Case O.R. showing incomplete calcification of the anterior longitudinal ligaments.

Roentgenograms of the spine made in the anterior posterior diameter often show three longitudinal streaks of increased density. The middle one is believed by Ehrlich[15b] to represent calcification of the ligamentum apicum. Careful study of preserved specimens has convinced him that the two lateral streaks are produced by an increased density of the joint processes of the posterior articulations

and of the joints themselves. We feel that calcification of the anterior ligaments, the ligamenta flava, the capsular, the supraspinous and the interspinous ligaments is the result of a reparative process secondary to the loss of normal articular support of the spine. The decalcification and partial absorption of the previously noted ligamentous ossification in the region of operative fusion is consistent with this view.

In our experience, in cases with associated involvement of the hip and shoulder joints, the disease in these joints resembles a severe atrophic arthritis. In a few instances there was considerable exostosis formation and calcification about the hip joints. This may represent a process similar to that described above as occurring on the ischia and pubes. It is interesting in this connection that Valentini[83] in 1899 believed that the loss of motion in the hip joints was due, not to an ankylosis between the head of the femur and the acetabulum, but rather to ossification of the joint capsule. Occasionally the temporo-mandibular joints are included in the ankylosing process. Ankylosis of the sterno-clavicular joints and of the shoulder joints proper, although reported, is rare.

Clinical Picture. Spondylarthritis ankylopoietica appears characteristically in young adults of the male sex, during the third and fourth decades of life. The onset may have been preceded by an acute or chronic infection of almost any sort, by one or more attacks of "acute polyarthritis," or by acute or chronic trauma to the spine. The onset may be acute but is usually insidious. In a few instances vague abdominal pains in the epigastric region and pains in and about peripheral joints occur. Although progressive stiffening of the spine may proceed for long periods of time without pain, this sooner or later makes its appearance, usually at first in the region of the sacrum and lower spine, but occasionally in the cervical region. The pain is subject to frequent fluctuations in intensity. As an early manifestation many patients complain of gradually increasing limitation of motion of the hips and lower extremities. Krebs[39] has pointed out that because of the lack of any very definite objective findings in the earliest stages of the disease, individuals suffering from it are often mistaken for malingerers and neurotics.

Examination of a patient in whom the disease is well established reveals the fact that the entire lumbar and dorsal spine is rigid. There is absence of the normal lumbar lordosis, and there may even be forward bowing in this region resulting in prominent creases across the abdomen. The upper part of the trunk is thrust forward. Abdominal type of respiration and decreased expansion of the chest are frequently quite noticeable. When the cervical region has become involved the head may be bent forward and held almost rigid on the neck. Kyphosis, when present, occurs in the cervical and upper thoracic regions. All grades of disability are encountered, depending on the duration and severity of the disease and whether

or not there is concomitant involvement of the hip and shoulder joints. Emaciation and loss of muscle tone is often very striking but is by no means an essential part of the picture. The latter finding has been given almost diagnostic significance by Grabowski.[27] In advanced cases we observed hypersensitivity, rigidity and spasm of the dorsal muscles and quite often muscle atrophy in the dorsolumbar region. Signs of root irritation are not uncommon.

FIG. 3.—Lumbosacral spine in an early case of osteoarthritis of the spine showing spur formation and intact sacro-iliac joints.

Other findings which should be mentioned are the by no means constant presence of low-grade fever, the equally inconstant presence of leukocytosis, and the not infrequent occurrence of anemia. The sedimentation rate, however, is almost invariably elevated far above normal during the active stages of the disease. Whether this statement holds true for very early stages of the disease is not known. The most important and frequent complications, in our experience, are pulmonary tuberculosis, iritis, pericarditis, and pneumonia.

Diagnosis. The diagnosis of spondylarthritis ankylopoietica may easily be suspected on physical examination alone. Vontz[84] maintains that a diagnosis in the early stages of the disease can and must be made on clinical grounds, because several months or even years may elapse before characteristic changes can be demonstrated by roentgenography. Koch[35] was able to study the early changes in the spine in one case. The first roentgenographic examination made one year after the onset of symptoms showed only a spotty atrophy about the posterior articulations in the lumbar region. Two years later, beginning ankylosis of these joints was demonstrated. Demonstration of changes in the sacro-iliac joints makes the diagnosis more certain. Lassen[43] asserts that these changes enable one to make a diagnosis very early. Unfortunately they are not specific and characteristic for this disease only. When involvement of the posterior intervertebral articulations is clearly demonstrated the diagnosis is established.

Roentgenographic Diagnosis. The usual Roentgen examination in sagittal and frontal diameters of the entire spine, plus special examinations of suspected areas in both obliques will demonstrate the anatomic lesions of the small joints and surrounding structures. It is important to bear in mind that the lesions may be well developed in one region while in others there may be only minimal involvement. The Roentgen findings according to the different stages consist in decalcification about the joints, blurring of the joint surfaces, narrowing and obliteration of the joint spaces, and areas of continuous calcification along the outer aspects of the vertebræ. Aside from those instances in older patients where there co-exists an hypertrophic arthritis, the vertebral bodies and intervertebral disks are well preserved and normal in contour.

Differential Diagnosis. The differential diagnosis of spondylarthritis ankylopoietica is principally concerned with hypertrophic arthritis of the spine. In the latter condition the onset of symptoms occurs, in 80% of cases, after the fourth decade of life (Krebs[38a]). The sedimentation rate is not elevated, and fever and leukocytosis are uncommon. In hypertrophic arthritis of the spine there is a degeneration of the intervertebral disk with narrowing of the intervertebral spaces, formation of exostoses about the edges of the bodies of the vertebræ and more or less marked wedging of the vertebral bodies. In advanced cases true bony bridging occurs. These changes are strikingly absent in cases of spondylarthritis ankylopoietica. There may also be present a coarse calcification localized to the anterior surface of the vertebral column, especially in the thoracic region. Changes about the costovertebral and posterior vertebral articulations are not commonly demonstrated in hypertrophic arthritis and when present consist in exostosis formation. Ankylosis of these joints does occur, but is never generalized. Ankylosis of the sacro-iliac joints, according to Saskin,[62] is present in the

majority of males by the fifth decade of life, hence examination of this joint offers little in the differential diagnosis.

The occurrence of only a slight elevation of temperature in the presence of a marked elevation of the sedimentation rate should be helpful in distinguishing spondylarthritis ankylopoietica from tuberculosis of the spine.

Brief mention should be made of other types of cases in which a painful rigid spine is the chief symptom. We have studied roentgenograms from 16 such cases, and in all instances there has been evidence of disease in the sacro-iliac joints. There were 2 cases in young adult males of true infectious spondylitis as described by Sternberg.[76] There was 1 case of rigid spine, also occurring in a young man, in which lesions could be demonstrated only in the sacro-iliac joints. There were 13 cases in young adult males in which the roentgenographic findings were limited to complete or partial fusion of the sacro-iliac joints with isolated but very prominent exostoses on the vertebræ. Recently Doub[14] has described a syndrome in which there is a noticeable lack of changes in the lower spine. It consists in the presence of a rounded kyphosis of the dorsal spine with narrowing of the intervertebral disks, and varying degrees of bone production, sometimes leading to complete bony fusion of the vertebræ.

Treatment. General hygienic measures are of the utmost importance. They should include adequate physical and mental rest, good nursing care, a complete high-vitamin diet, ultra-violet irradiation (natural or artificial), correction of constipation when present, occupational therapy, and a congenial atmosphere. When feasible, patients should be spared the rigors of our northern winters. They will profit considerably from extended periods of residence in the warm even climate of the Caribbean or the dryer climate of our Southwest. In either case we feel that worthwhile results can be achieved only if the time spent in these regions is reckoned in months, or better in years, rather than in weeks, and if other forms of treatment are continued under careful medical supervision.

Salicylates contribute considerably to the comfort of the patient and are a time-honored remedy for rheumatic conditions. Pyramidon is even more effective but should be used with caution and only if the granulocyte count is constantly watched. The administration of calcium in the form of calcium gluconate is in our opinion desirable in the presence of the extreme bone atrophy met with in this disease, and in spite of the tendency to calcification of ligamentous structures. Gold salts have been recommended. Arsenic compounds, iodides, colloidal sulphur and other drugs have had their advocates.

Anemia if present should be corrected by iron or iron and liver therapy. Transfusions of whole blood will not only raise the blood hemoglobin, but also, in some instances, will result in an improvement in the patient's condition greater than can be attributed solely to the improvement in the blood picture.

Vaccines, whether autogenous or stock, are in our opinion uncertain in action and any favorable effect from their use is for the most part to be attributed to a non-specific action. Fever induced by foreign proteins such as typhoid vaccine or by mechanical devices may induce striking remissions, but this type of therapy should be used with the utmost caution, and only when the patient's general condition warrants it.

Infected foci should be treated and, where possible, removed. It should be borne in mind in this connection that untimely efforts in this direction may result in a severe exacerbation of the disease.

The intelligent use of physiotherapy is of the greatest importance and should be conducted along conservative lines. Local heat administered by long and short wave equipment supplemented by gentle massage contributes greatly to the patient's sense of well-being, prevents muscle atrophy and contractures, and promotes restoration of normal muscle tone and function if the latter is already impaired. Carefully supervised active and passive exercises with or without balneotherapy are helpful in achieving the same ends. Thomsen[80] has advised the use of a tight abdominal binder to increase thoracic respiration. Deep breathing exercises are recommended by Tyson[82] who also advises his patients to learn to sleep on their backs.

Orthopedic procedures should be directed primarily to relieving strain on the inflamed structures and to the prevention and correction of deformities. Swaim[78] found that the latter could be achieved by the use of plaster jackets, while good position once attained could be maintained by leather jackets.

Prognosis. Although spondylarthritis ankylopoietica may cease to progress at almost any stage in its development, it is usually slowly progressive, subject to remission and exacerbation, and gives the patient little peace until at the end of 10 or 20 years bony ankylosis is established, and there is cessation of pain. The amount of permanent crippling will depend upon the timely institution of orthopedic measures in an effort to minimize deformity and prevent ankylosis of the hip or other peripheral joints when they are involved. Ködderman[36] has drawn attention to the occurrence of "*formes frustes*," in which there are few symptoms and in which the therapeutic results are excellent. Rumpel[60] has pointed out that the presence of a rigid thorax favors intercurrent pulmonary infection as a cause of death in patients with spondylarthritis ankylopoietica.

Discussion. *Incidence:* Schmorl[66] found 8 cases of spondylarthritis ankylopoietica among the 10,000 specimens of vertebral columns in the Dresden Collection, an incidence of less than 0.1%. In Bachman's[4] series of 2561 Roentgen ray films of the spine there were 41 clear-cut cases. Among 640 films which Haenisch made available for study by Bachman there were 6 cases of the disease.

Taken together Bachman's figures indicate an incidence of 1.5% in a large series of Roentgen ray films of the spine taken for various reasons. Krebs,[38a] among 202 cases of stiffness of the spine, found 21 cases of spondylarthritis ankylopoietica; the rest he classified as "spondylose deformans." It is obvious from the above that this disease is not rare, but that its true incidence must be less than 0.1%.

Seventeen of our 20 patients experienced their first symptoms prior to the thirtieth year of life. The earliest age of onset was 18, and the latest 40. In Fischer's[17] series of 100 cases, 44 began in the third decade of life, 32 in the fourth decade, 13 in the fifth decade and 6 in the sixth decade. Three cases date from the second decade. In Krebs'[38a] series of 21 cases, 62% began in the third and fourth decades of life, while in his series of 181 cases of "spondylosis deformans" only 20% experienced their first symptoms in those decades.

There is a striking unanimity of opinion as to the sex incidence of spondylarthritis ankylopoietica.[17,20,25,38a,58] In our series of patients there were no females. All of Fischer's[17] 100 cases were in males. Buckley's[9] series contains the highest incidence of cases in women. Six out of 60 (10%) of his cases occurred in females. He was unable to discover definite endocrine disturbances among these.

Since the diagnosis of spondylarthritis ankylopoietica has been placed on a fairly firm basis, there has not appeared, to our knowledge, any good evidence that the disease is familial, although occasionally two members of the same family may have the disease. Many authors, especially those who believe that the disease represents atrophic arthritis as it affects the spine maintain that hereditary constitutional factors are of great importance. The sex and age distribution of this disease indicates that fundamental constitutional factors, whether they be of an endocrine nature or not, are important in determining susceptibility to it.

Since the first paper of Fraenkel,[19a] trauma has been discussed as a possible etiologic factor in spondylarthritis ankylopoietica. Krebs and Vontz[39] have called attention to the fact that the disease may develop asymptomatically until an incident of trauma has occurred. Wehrsig[85] maintains that trauma, acute or chronic, is a factor in 25% of cases. By and large, trauma has not been a prominent feature in our records.

Proebster[58] believes that acute or chronic chilling is important in the etiology of spondylarthritis ankylopoietica and calls attention to the fact that many patients date the onset of their disease from war service. One of the patients in our series (E. G.) was quite certain that this was true in his case. Wolff,[87] however, is skeptical of these stories. He investigated a number of such cases and found that in almost every instance the patient had had either episodes of pain in the spine prior to his World War service or one or more attacks of acute peripheral arthritis.

Evidence for the Infectious Nature of Spondylarthritis Ankylopoietica.—The etiology of spondylarthritis is as obscure as that of atrophic arthritis. They are both, presumably, infectious diseases. In both the sedimentation rate is elevated during the active stages. There is usually a low-grade fever and frequently a slight elevation of the white blood count. These last are not marked unless there is an active infectious complication such as pneumonia, pericarditis or pulmonary tuberculosis. The sedimentation rate, however, may be extremely high in both diseases even when no active local infection can be discovered. In both conditions the paranasal sinuses and teeth are often found to be in an unhealthy state, but whether they should be considered as harboring primary and etiologically significant foci of infection, or whether their tendency to become infected is merely evidence of the generally debilitated state of the patient cannot be definitely asserted. The lesion in the posterior intervertebral joints is certainly that of an infectious process. Lux,[46] who believes that focal infection causes spondylarthritis ankylopoietica, has called attention to the severe exacerbations which accompany intercurrent infections. The same, however, occurs in diabetes and pernicious anemia. Wolff[88] stresses the point mentioned above, and as further argument cites the frequency of eye complications and anemia, as well as the therapeutic response to removal of infected foci, the administration of pyramidon, and treatment with gold salts. Five of our cases developed after acute infections.

Originally Marie[48] felt that gonorrhea had nothing to do with the disease, but he later[50] revised this opinion and stated that gonorrhea could cause typical spondylose rhizomélique. Sol[73] believes that the spinal involvement seen in cases of chronic gonorrhea is characteristic of spondylarthritis ankylopoietica. Wolff[87] and Bottoli[6] believe that chronic gonorrhea is of etiologic significance. Although several of his patients had had gonorrhea, Touw[81] does not believe that there is any relationship between the two conditions. In our series of cases, one (J. C.) definitely followed acute gonorrhea, another (O. R.) was associated with a second attack of gonorrhea or reactivation of an old infection. We believe that gonorrhea may be causally related to spondylarthritis ankylopoietica, but probably not in a specific sense.

There were present consistently, in the urine of 14 of our patients, occasional to 10 to 15 white blood cells per high power field. This fact indicates that a low-grade urinary tract infection, gonorrheal or otherwise, is frequently present in this disease. Forestier[18] believes that the primary focus is in the genito-urinary system, and that toxic products are drained to the pelvis and spine by way of the lymphatics. Kienböck[33] relates the disease to tuberculous infection of the genito-urinary system. No pathologic evidence has yet been presented to substantiate either theory.

Although most authors have inclined towards the view that we are

dealing with an infectious disease other theories have been advanced. Steffens[75] believes that spondylarthritis ankylopoietica results from a fundamental endogenous metabolic or endocrine disturbance. A few years ago there was a flurry of interest in a possible relationship between parathyroid dyscrasia and spondylarthritis. Ssamarin[74] reported a group of 55 patients on whom he did parathyroidectomies. The pre-operative serum calcium values were remarkably high. Leriche and Jung[44] reported parathyroidectomies done on 3 patients with abnormally high serum calcium values. Funsten[21] treated various types of "spondylitis" by parathyroidectomy and felt that the results were satisfactory. Compere[11] was unable to discover any evidence of dysfunction of the parathyroid glands in cases of spondylarthritis ankylopoietica. The authors agree with Welti[86] that the figures given by Ssamarin are open to question, and that at present there is no convincing evidence that the parathyroid gland plays a rôle in the ordinary case of spondylarthritis ankylopoietica.

Pulmonary tuberculosis is a serious complication of spondylarthritis ankylopoietica. One of the patients whose case was reported in Fraenkel's first paper[19a] died from this disease. According to Proebster,[58] Poncet, in 1903, reported 3 cases of "spondylose rhizomélique" which he believed were the result of tuberculosis. Fischer and Vontz[17] found active pulmonary tuberculosis in 3 of their 100 cases. Like Krebs[38a] they found a lower incidence of this complication than anticipated. The high incidence of pulmonary tuberculosis in our series of cases (25%) is partly to be attributed to the fact that the Desert Sanatorium attracts a considerable number of tuberculous patients. Among the 201 cases of atrophic arthritis, however, the incidence of active pulmonary tuberculosis was only 2½%. In none of the patients with spondylarthritis ankylopoietica and active pulmonary tuberculosis was the tuberculosis diagnosed until at least 1 year after the onset of symptoms in the spine. Two of these patients eventually died of the pulmonary disease. No patients with spondylarthritis developed active pulmonary tuberculosis while at the Sanatorium. Two patients in our series showed Roentgen ray evidences of healed apical tuberculosis.

Recently Scott[69] has postulated that spondylarthritis ankylopoietica is the result of active infection, usually tuberculous, of the sacro-iliac joints. Kienböck[33] has stated that the disease is an exudative synostosing form of joint tuberculosis, the infection proceeding to the spine by way of the lymphatics from a latent tuberculosis of the genito-urinary tract. Neither author offers any substantial evidence to support his view. Fischer and Vontz[17] tested patients with subcutaneous inoculations of tuberculin. The reaction was never focal and rarely general. Assman[3] concluded with Fraenkel that the pulmonary disease is not causally related to the disease in the spine, and is either secondary to it or merely incidental. The authors of the present paper are in accord with this view.

The incidence of iritis in patients with spondylarthritis ankylopoietica is not very well known. Fischer and Vontz[17] observed its presence in 3 of their series of 100 cases. Wolff[87] found it had been present in 6 of 15 cases. In Golding's[25] series of 124 cases, it had been present in 5.6% of the cases. It was present at some time during the course of the spondylarthritis in 5 of our cases, that is, in 25%. In the 201 cases of atrophic arthritis, the incidence of iritis was 2%, while among the 95 cases of hypertrophic arthritis there were no cases of iritis. Sol[73] feels that iritis is particularly characteristic of the spondylitis which results from a chronic gonorrheal infection. In none of our cases with iritis was there any evidence of gonorrheal infection. It is of interest and perhaps suggestive of a "rheumatic" basis for the iritis that in 1 of these patients (R. Q.) there was definite evidence of disease of the mitral valve, and that 2 other patients (E. H. and W. B.) each had a pericarditis at the time of at least one of their attacks of iritis. Teschendorf[79] and Kraupa[37] believe the iritis is merely a sign of a general infection. The former took roentgenograms of the spine in a series of cases of iritis and discovered 6 cases of frank spondylarthritis ankylopoietica, and 3 instances, in patients who were entirely symptom free, where changes were present in the spine characteristic of the disease. Ascher[2] calls attention to the grave prognosis in the iritis which occurs with spondylarthritis. Kunz,[41] found evidence of tuberculous infection in only 1 of 7 cases with iritis. None of the cases in our series with active or inactive tuberculosis had iritis. That iritis is an important complication of spondylarthritis ankylopoietica is certain, but its relationship to the process in the spine has yet to be defined.

Spondylarthritis ankylopoietica can develop in patients with a typical atrophic arthritis (Proebster). Chalmers[10] believes that "spondylarthritis atrophica" is a manifestation of rheumatoid arthritis. Fischer[17] found evidence in his study that suggested a possible relationship between acute rheumatic fever and spondylarthritis ankylopoietica. In 11 of his 100 cases there was frank valvular disease of the heart. In 4 of these cases there had been an acute polyarthritis prior to the onset of the spondylarthritis; in 2, there had been a gradual swelling of certain peripheral joints simultaneously with the development of the spinal disease. Krebs and Vontz[39] cite a case which followed acute rheumatic fever with involvement of the aortic valve.

Two of our patients (R. Q. and R. C.) had had rheumatic fever some years prior to the onset of the spondylarthritis. One of them (R. Q.) had a definite lesion of the mitral valve. In 3 cases there was clinical evidence of atrophic arthritis of the small joints of the extremities (J. C., W. K., and H. M.).

Whether spondylarthritis ankylopoietica should be classified as a disease sui generis or be considered as the spinal form of atrophic arthritis is difficult to decide. The fact that the majority of patients suffer from active disease of the spine for many years without

involvement of the small joints of the extremities seems to indicate that the two conditions are not the same. In our opinion spondylarthritis ankylopoietica belongs to the group of so-called rheumatic and rheumatic-infectious diseases. Its striking predilection for members of the male sex sets this lesion in a class apart, at least until the etiology of this and the other rheumatic diseases is clarified.

Summary. 1. We have reviewed the development of the concept of spondylarthritis ankylopoietica as a disease distinct from "spondylitis deformans."

2. A statistical study of 20 cases of this disease has been presented as a basis for discussion.

3. The pathologic anatomy of spondylarthritis ankylopoietica has been described with particular reference to the changes in and about the pelvic girdle.

4. The clinical picture and the problems of diagnosis and treatment have been presented.

5. The significance of iritis and tuberculosis as complicating conditions has been discussed.

6. We have reaffirmed the infectious nature of spondylarthritis ankylopoietica, at the same time emphasizing the fact that constitutional factors are fundamental as shown by the age and sex distribution of this disease.

7. The relationship of spondylarthritis ankylopoietica to the problem of rheumatism has been discussed.

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NUTRITIONAL ASPECTS OF THE TREATMENT OF ARTHRITIS.

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In a presidential address before the American Rheumatism Association,[16b] one of the present authors endeavored to reduce to a brief compass a few principles and broad considerations illustrative of

the clinical philosophy which he holds toward the field of arthritic diseases in general. The generic nature of the problem was emphasized and also the therapeutic corollary that treatment of the arthritic should proceed along many lines. The response to this effort has suggested that a further exposition of some of the considerations there advanced might be of value to those who treat arthritics.

There is still much contemplation of disease as a process involving one organ, one system or one mechanism alone, whereas many chronic disease states present an interwoven pattern of disturbances in several parts of the body, no single one of which disturbances is always dominant. This is especially true of arthritis. The number and variety of therapeutic considerations to be thus entertained toward the problem of arthritis is, indeed, so considerable that, in most attempts at exposition of them, only titular references can be made because of limitations of space. Furthermore, there is a general, and perhaps natural, assumption of familiarity with details of therapy falling under significant but apparently obvious captions such as local rest, systemic rest, betterment of circulation and optimal nutrition, which is not always justified, so far as effective application to the treatment of arthritics is concerned. For these reasons, we are persuaded that recommendations of therapy made along generic lines often fall short of their purpose and that the need of emphasis upon detail is greater than might be supposed. We also believe that therapy should be more pointedly directional than is usually the case.

The syndrome of the chronic arthritides is now universally recognized as consisting of at least two great types, namely, atrophic or rheumatoid arthritis, and hypertrophic or osteo-arthritis. Chronic arthritis at large, however, was well defined by the American Committee for the Control of Rheumatism[1] as a systemic disease with joint manifestations and in many cases of the true syndrome, especially in the atrophic group, the joint disturbances are minimal, the disability being chiefly in the tendons, fibrous tissues, muscular tissues, nervous system or elsewhere. Such instances emphasize the fact that the syndrome concerns primarily the mesodermal tissues as a whole and that the term "arthritis" is either a misnomer or inadequate. The term "rheumatism" covers the field rather better, although somewhat vaguely, and it is possible that we may later come to some such definition as "mesodermosis," which would carry a desired implication of wide distribution because of chief involvement of the derivatives of one of the blastodermic layers of the embryo. The use of this term here is only illustrative, but the point of view suggested by such nomenclature emphasizes the fact that many factors influence the several expressions of the syndrome.

The full nature of the problems presented by arthritis has not

yet been revealed with finality and all of the links in the chain between suspected etiologic factors and the developed disease have not been forged. We are satisfied, however, that enough is known to justify the statement that the syndrome of arthritis is susceptible of fuller control, both preventive and arresting, than is yet exercised toward it, except in a few selected centers of study. Even in some such highly regarded centers the emphasis has often been on a few single factors of etiology or therapy, to the incidental or intentional exclusion of a host of considerations which may be equally significant in the care of the patient. Gregg[8] recently remarked "Some of the finest teaching can take place when there is much to discover and but little as yet to indoctrinate," and to few medical fields is this thought more relevant, perhaps, than to that of rheumatoid disease. In a syndrome of uncertain origin so varied as is arthritis it is next to futile to expect instant clarification by a laboratory or clinical "tour de force." Certainly none has been forthcoming to date. It follows, therefore, that there is both propriety and necessity in scrutinizing each component of therapy in relation to the whole and in weaving them together.

There has been needless controversy as to which factors of therapy should be stressed. The fact is that all well-considered factors should form part of a coördinated approach and should be played upon as a keyboard rather than separately as in the sounding of a single note. For these reasons the present contribution will enter into greater detail regarding some of the therapeutic recommendations referred to above. As it is obviously impossible to cover the therapy of arthritis within the compass of a brief article, attention will therefore be confined chiefly to one phase of therapy which, in particular, often seems to be imperfectly grasped, namely, the application of nutritive principles to the physiologic needs of the arthritic. This will be discussed, however, not as a separate topic but in connection with that balanced outlook which envisages all of the deviations from normal presented by the arthritic as integral parts of the clinical problem. It is especially relevant at present to draw attention to nutritional and metabolic considerations since the reaction, now well under way among the profession, against that domination which the doctrine of focal infection long held over this field, justifies and indeed necessitates consideration of other factors suspected or known to have influence. The view is indeed developing in some quarters that the phenomena of arthritis may conceivably reflect, through such factors as infection, exposure, nervous strain, or faulty nutrition, a disturbance of equilibrium of the central nervous system and especially of the hormonal balance of the "master tissues." The peripheral expressions of such imbalance within the mesodermal tissues might be expected to be more or less symmetrical, as they often are in arthritis. With such an outlook, nutritive factors would obviously be only one of many groups of

factors involved, but they deserve consideration because of relationships and influences known to exist and to be open to modification. It is not too much to expect that some clinicians, inclined hitherto to overlook or minimize these factors, will now weigh them more carefully.

The broad bases of nutrition underlie several clear-cut and many less-defined clinical syndromes but appreciation of these relationships is far from widespread. Even the term "nutrition" still carries to many the implication, in the field of arthritis, of gross departures from average weights; namely, over-nutrition or under-nutrition; that is to say, adiposity or emaciation. Because of this limited concept, almost the only concern exercised is that the emaciated arthritic be fattened and the obese arthritic reduced. On broad grounds this principle is usually justified, so far as it goes, but between these extremes there is a wide sphere of influence to which scant attention is given. Furthermore, even the principle of fattening the thin and thinning the fat may not be prescribed indiscriminately, and in some instances in which imbalance of nutrition exists in less obvious degree, definite harm may be done to the arthritic subject, usually suffering already from many handicaps.

Nutrition shares with heredity the function of determining the constitution or general capacity of the body for maintenance of itself. Experimental animals bred from standardized stock may be made to develop into physically superior animals by providing optimal rations, or into dwarfed creatures with shortened life spans by reducing certain components of the diet to suboptimal levels. The development of deficiencies in progeny or individuals may be significantly influenced, even precipitated, by coincident infections and by altered physiologic mechanisms. Chronic nutritional deficiencies may permit pathogenic agents, such as bacteria, to become immediate factors in a given disease process. The reciprocal relationship of infectious factors and dietary adequacy appears to have an important bearing upon the arthritic. The growth of bacteria in tissues not only diverts certain materials required for such growth from their normal function in the maintenance of tissue, but also discharges into the circulation "toxic" products which combine for defensive purposes with still other substances, such as amino acids, to form inert products. These conjugated products are then eliminated from the body with a consequent net loss of various materials to the economy as a whole.

In this light, arthritis can be visualized as a disease of extraction, by virtue of the demands made by the metabolism of bacteria upon vitamins and tissue ingredients, as much as, or more than, one of invasion by bacteria as has so long been generally held. Dietary inadequacies may, further, lead to apparently minor gastro-intestinal disturbances which, only after years, eventually reflect the picture of a deficiency syndrome. Castle[2] has shown that an

asymptomatic abnormality of gastric secretion may induce a state of dietary deficiency in spite of the "adequacy" of the diet.

Not only deficiencies but also relative excesses of certain dietary factors lead to pathologic states. Attention may be called to the production of nephrosis by cystine or diets low in vitamin B;[4] the exaggeration of nephritis by diets high in nucleoprotein,[14] in contrast to simple protein; the production of beri-beri by excessive carbohydrate on a suboptimal intake of vitamin B_1;[5] the production of cataract by diets high in galactose;[13] the development of rickets by a high caloric intake on a basal diet otherwise adequate or low in vitamin D.[12]

Funk[6] and McCarrison,[11] as well as Cowgill,[3] have concluded that there is apparently a balance between the need for and the utilization of vitamins on the one hand and, on the other, the amounts of the other constituents of the dietary, such as protein and carbohydrate. These considerations imply, not that carbohydrate, for example, is "toxic," but rather that the body requires a minimal quota of thiamin and riboflavin for the enzymes essential to the metabolism of glucose. If the amounts of glucose exceed an optimal level the quota of vitamins is drawn upon, leaving lesser amounts to meet endogenous requirements.

There is no complete parallelism of arthritis with any known specific deficiency disease. Many cases present graphic evidence, however, of disturbed metabolism of a kind which could be accounted for upon such a basis, in part at least. These evidences include bone and muscle atrophy, anemia, low plasma protein, infiltration of fibrous tissue, degeneration of cartilage, low basal metabolism, decreased saturation with vitamin C, reduced glucose tolerance, diminished range of variability of skin temperature and disordered immunity.

The view that hypertrophic arthritis represents largely degenerative processes, probably involving errors of metabolism referable or amenable to nutritional influences, appears easy of acceptance. That atrophic arthritis, hitherto usually regarded as referable to infectious factors only, may be comparably influenced by nutritional factors, has been apparently more difficult of acceptance. There is as much reason, however, for the view that imbalanced nutrition may, with other factors, pave the way for invasion of bacteria conducive to arthritis in the young, as there is for the view that it may with other factors pave the way for "degenerative" factors conducive to arthritis later in life.

Again, and more specifically, it is becoming abundantly clear that along with the so-called "true" arthritides, atrophic and hypertrophic arthritis, with which fibrositis is also usually grouped, we have to deal with affections of joint structures or interarticular structures, sometimes classified as "arthroses." To what extent it is justifiable to segregate these states and to what extent they merge with the true arthritides is not finally determined, but it is

certain that they are related to the arthritic syndrome. The particular relevance of this is that in some such arthroses, hypothyroidism is demonstrably present, and, indeed, a somewhat lowered metabolic rate is met with in about 30% of all arthritics as a group. In some cases part of the lowered basal rate may derive from closure of some of the capillary beds, particularly in muscle,[16] but the benefits following thyroid medication are so clear-cut in other instances as to leave no room for doubt that the thyroid itself is actually involved at times. Acceptance of this premise requires that metabolic processes at large, both exogenous and endogenous, be weighed in the etiologic and therapeutic scale, and that everything which influences intermediary metabolism should have consideration. In this sense, not only the quality and the proportions of the foodstuffs but the amount could be expected to have a significant influence, and there is, indeed, evidence that in some cases of arthritis a difference of some 350 calories may, under perfectly balanced conditions, be influential.

Although, as remarked above, there is no final evidence justifying classification of arthritis as a disease of dietary deficiency, recent Roentgen ray studies of the gastro-intestinal tract in 400 arthritics by Spackman *et al.*[19] reveal that part of the picture characterizing experimental deficiency states in animals in respect to the vitamin B complex is to be seen with striking uniformity, almost as a pattern, in arthritics as compared with normals. The elongated and dilated gut induced by McCarrison *et al.*[11] in monkeys is closely simulated in arthritics, and there is general agreement that this situation is referable to faulty nutrition and secondary imbalance of the autonomic nervous system. One of the therapeutic corollaries to this state of affairs is the institution of optimal nutrition.

Optimal nutrition is a relative or comparative term, however. It can relate only to the best nutrition for the given subject and it is necessary to define the standards on which optimal nutrition may be predicated. Optimal nutrition in the broad sense implies maintenance of tissue in a milieu wherein the highest level of function can be exercised. Inasmuch as the function of tissues varies with a number of factors, the only type of prescription which can be presented is one which directs consideration to the particular needs to be met. For example, dietary supplies optimal for a normal adult subject may be inadequate for the person whose capacity for absorption is limited by gastro-intestinal dysfunction. Similarly, a diet adequate for the requirements of an organism previously well supplied with essential dietary materials is inadequate for the organism which has been poorly supplied or whose requirements for specific substances have been increased by the presence of competing forms, *i. e.*, bacteria or parasites. It is equally true that there are needs for specific dietary materials and favorable relative proportions of them during periods of modified physiologic function, such as occur in disease, and it is generally recognized that there are

increased demands during periods of increased energy output. Age and size also introduce variables. It is thus apparent that the establishment of optimal nutrition is not a matter of providing food elements in a stereotyped manner, but that it requires critical consideration of the particular favorable balance to be achieved, as well as of the factors operative to prevent this balance.

There is another aspect of the problem, exemplifying the special dietary adjustments required for achieving optimal nutrition in the arthritic, which is frequently overlooked. This concerns the low-grade edema presented by many arthritics. The whole significance and mechanism of this condition is not fully understood. Part of the "edema" may be referable to low plasma proteins but not all of it. In any event, there is small doubt that some of the symptomatology of the disease, especially some of the pain and stiffness, is referable to this "tissue edema," as can be easily demonstrated in suitable subjects.[18] Thus arthritics may experience surprising benefit immediately following major operations, as is now familiar to many observers. Among the several conspicuous features associated with such remissions is the necessarily sharp curtailment in the caloric value of the dietary intake.

A diet which supplies less than the caloric requirement, if practised for a few days, may induce striking changes in the symptomatology of arthritis, particularly as regards swelling, pain, and limitation of motion. This is most likely to be found in patients under adequate conditions of rest and protection, and especially in those in whom infectious factors appear to be minimal or absent. This is a procedure fraught with great danger to the sick arthritic, however, and extreme application of it has sometimes brought discredit to such practice.

It should be noted that such practice, nevertheless, has become in many places a more or less routine measure of treatment. In one institution, treatment of arthritics is usually initiated by free catharsis accompanied by restriction of the diet to orange juice for 3 days. Routine practice of this sort is not justifiable and yet criticism can well attach to any attitude of the profession as a whole which ignores the nucleus of truth in such methods and forces patients to experience unwise applications of them. Some analogy to this is to be seen in that attitude on the part of orthodox medicine which ignored the benefits inherent in physical therapy, especially massage, and so drove countless persons to the receptive arms of osteopaths and other cultists.

von Noorden,[15] Gerson[7] and others have employed raw vegetable diets in the treatment of various diseases, including arthritis. The clinical improvement noted on this dietary regimen has been largely attributed to the fact that diets so constituted are low in sodium salts. Hare[9] has recently employed a similar dietary regimen under controlled conditions in a series of 12 cases, as follows. Rations of uncooked foodstuffs consisting of approximately 145 gm.

of carbohydrates, 35 gm. protein and 143 gm. fat were supplied for a period of 2 weeks. Following this period, cooked foodstuffs of similar content were provided. In 8 of 12 instances marked improvement resulted in the soft tissue manifestations. Two cases experienced temporary benefit and the remaining 2 cases obtained no relief. The toxic symptoms and the bone lesions did not appear to be greatly modified. The favorable clinical result was associated with a rapid loss of tissue water during the first week of treatment. This response is attributed in large measure to a low sodium intake. Some emphasis was also placed upon the provision of adequate protein, fat and vitamins B and C.

The use of similarly modified diets which are relatively low in carbohydrates has led Pevsner *et al.*[17] to the view that part of the clinical improvement upon such a regimen is to be attributed to a nonspecific desensitization of the tissues to various undefined entities. Leporsky[10] has noted clinical benefit following the use of diets which provide a limited supply of total calories. These observations are cited to illustrate the fact that, whereas different views are expressed as to the mechanism involved, there is rather widespread recognition of a significant therapeutic effect to be obtained by modified rations in arthritis.

Inspection of these various dietaries, however, reveals clearly that they are characterized by under-maintenance or mere-maintenance levels and that whatever other factors may be concerned, allegedly or otherwise, they all promote elimination of tissue fluids. This influence must of necessity bring about the consequences now to be referred to.

Turning, therefore, to the "edema" under discussion, it can be said with confidence that under appropriate conditions it can be favorably influenced or aggravated by varying the proportion of foodstuffs in the dietary which contribute to retention of water within the body. The foodstuff most influential in this connection is carbohydrate and for every gram of it stored there is also retained from 3 to 4 gm. of water. Storage of 1 gm. of fat leads to retention of only about 0.1 gm. of water, and protein leads to little or no retention of water, since it is rarely stored except after a debilitating state such as typhoid fever when a deficiency is to be made up. The catabolism of protein leads to the formation of materials which require water for excretion. Furthermore, in arthritis the plasma proteins may be low, especially albumin, so that part of the edema, though not all, may be referable to this basis, as remarked above. When this is the case, additional protein is necessary to correct the faulty colloid osmotic relationships. Whatever the full explanation of this low-grade edema of arthritis, importance attaches to all mechanisms influential in reducing it. Other measures contributory to this same end are purgation, sweating, possibly a low salt intake, certainly rest in recumbency, and massage. The first two mentioned form the basis of much of the therapy exhibited at the spas

of Europe and are not without danger. Massage is also a two-edged tool and must be used with care. None of these can be persisted in for extended periods. Furthermore, depletion of tissue water in these ways is largely negatived unless continued restriction of fluid be observed. Control of tissue water by diet, if exercised intelligently, can be carried on more or less continuously and with less regard to the fluid intake. Indeed, on a mere-maintenance or submaintenance diet the food intake may be entirely liquid in form and yet the economy will lose water. The most immediate and graphic effects in reducing the above edema, with or without dietary influences, are probably to be seen in those atrophic arthritics who have been "carrying on" in spite of poor health and are then abruptly put to bed. Rest in recumbency promotes passage of fluid from tissues into vascular channels and may alone inaugurate changes within 3 days, often evidenced by a decrease in tissue tumefaction in the hands, revealing atrophied tissues and tendons previously hidden, as pointed out by Scull and Pemberton.[18] If accompanied by a diet adequate in calories and protein, relatively high in fat and low in carbohydrate, this effect is intensified. The same dietary influence can often be observed in ambulant patients, though obviously handicapped then by adverse gravitational and physiologic factors.

It may fairly be said, therefore, that most arthritics will experience benefit upon a diet which provides an adequate supply of calories and is optimally balanced with respect to various components, along the lines discussed. Thirty calories per kilo afford a good starting point at rest except in those who are overweight, when this allowance is too high. In addition to other advantageous influences, rest in recumbency is of great importance in cutting down the caloric needs of the individual and permitting a lower intake *in toto*.

The diet should contain at least 1 gm. per kilo weight of protein of good biologic quality. This quantity has been found by the trial and error method to keep most patients in nitrogenous equilibrium. It is evident that the conspicuously underweight individual should be given more protein than this amount, whereas the grossly overweight patient may be given less. Emphasis should be placed upon the quality or source of the protein, since all proteins are not equivalent in the property of supporting growth, or presumably, in providing for the regeneration of wasted tissues. In further conformity with the general principles enunciated above, carbohydrate should supply from one-third to one-half of the remaining calories needed and fat should supply from one-half to two-thirds of the balance, unless intolerance for fat be manifested. In the average unrestricted dietaries of most persons these proportions are roughly reversed, especially in the lower wage groups. Along with the above there should be an abundance of inorganic salts and vitamins. Accessory feeding of the latter is usually indicated.

Some influence from the broad dietetic changes above discussed may perhaps be observed in most cases of arthritis but this influence can be of true therapeutic value only when "drags" operating in an opposite direction have been removed or controlled. The more drastic measures of purgation and sweating, long advocated for arthritics, as well as salt restriction, are usually not necessary and should be reserved for sthenic cases.

It must be emphasized again that nutritive factors tending toward the reduction of tissue edema do not necessarily affect the basic cause or causes of arthritis. They may, in part, do this, but in any event they often definitely contribute toward betterment of a condition of the tissues which demonstrably aggravates the arthritis for purely physical reasons, and probably constitutes an important part of the true syndrome.

Enough has probably been said to illustrate the nutritive aspects of the therapy of arthritis and to explain why a casual approach to treatment as a whole, not to mention the nutritive aspects of it, so often fails of results. Medical literature contains many references to the "reserves" or "recuperative powers" of patients. These terms carry indefinite connotations, however, and there is practical, therapeutic advantage in all serious cases of arthritis in thinking more precisely in terms of the several actual dysequilibria in the major systems of the body which can frequently be shown to exist and to be open to amelioration. Among the dysequilibria thus encountered is that of faulty nutrition, using this term in a refined sense of the word. This constitutes a very frequent finding in arthritics. Even when no obvious or gross error is observable, modifications in the food intake along the lines and within the limits discussed may prove very beneficial. To apply these principles alone, however, without concern for other factors which are known to be operative basically, in many cases at least, such as infection, anemia, under-nutrition, reduced plasma proteins, gastro-intestinal dysfunction or nervous imbalance, may result not only in failure to obtain the desired improvement but possibly in further aggravation of the conditions present and in consequent discredit to physiologically sound procedures. Unless opportunity be given for dislocated processes of physiology to return toward normal by lessening the burdens on them from whatever cause, they remain dislocated. Removal of the original cause of this dislocation may no more correct the end results than repair of a faulty switch after derailment of a train restores the cars to the track. Minor factors, uninfluential alone, may suffice to perpetuate a dislocation originally brought about by very different agencies.

An easy or early demonstration of a reduction in tissue edema through the combined or separate influences of rest, sound dietetics, the sweat process, and so on, should not necessarily imply that any of these measures can be persisted in or applied routinely. Which

one, if any, should be stressed is entirely a matter of clinical judgment. Experience with the operation of these influences illuminates sharply the fact that a full perspective of the field is a requisite to adequate therapy. This perspective is not to be obtained through morphologic or *in vitro* studies alone; clinical developments can be equally informing. It is to this complex state of affairs that the problem of nutrition must be referred in the care of arthritics.

One of the confusing problems confronting the general practitioner is the apparent conflict among students of arthritis as to the alleged merits of therapeutic measures, on the one hand, and the paucity of proven etiologic factors, on the other. Thus, one group of students expresses the view that certain therapeutic measures are of great value, whereas another group counters that such measures should not be applied because there is no adequate evidence of their therapeutic relation to the disease. It is further stated by some that atrophic and hypertrophic arthritis are progressive diseases in that each disease runs its course regardless of the type of therapy instituted. The former disease is sometimes said to be arrested only when ankylosis is reached and the tissues are no longer reactive; whereas the latter, as manifested in Heberden's nodes, is arrested when calcification of tissue prevents further response.

While it has been repeatedly emphasized that arthritis is a systemic disease, the classification of the syndrome into two or more kinds of arthritis upon the basis of the articular lesions may erroneously limit attention to this aspect of the patient's difficulty. The patient, despite the fact that he may also suffer from anemia, nutritional imbalance and nervous manifestations, is actually told by some students of the subject that, because he has an atrophic lesion in his joints which cannot be undone, he has a hopeless condition, about which nothing of real importance is known and therefore nothing can be accomplished. Indeed, according to this negativistic school, a patient cannot be classified as an atrophic arthritic if his joints get better. By the same token, the patient with hypertrophic arthritis is advised, because he presents characteristic bony overgrowths, that he need not be concerned with focal infection in his teeth, since the removal of such infection has no proven relation to and therefore cannot cure the articular disorder.

It seems incredible that these points of view should have such wide acceptance among physicians whose declared purpose is to care for the whole of the patient who has rheumatic disease. This false philosophy arises from a well-intentioned attempt to be critical. A little learning, however, may be a dangerous thing. One should drink deeply or not at all at the Pierian Spring.

The practical deduction from these differences of opinion is that consideration of the syndrome of arthritis from one pathologic aspect or from an incomplete etiologic aspect alone, is inadequate for clinical purposes. This would make little difference, except academically, if it did not lead to undesirable limitations of treatment.

This definitely restrictive influence in arthritis results in a wrong application of the "all or none" law of physiology, that the response from a given stimulus must be maximal or it is without existence. The uncritical application of this notion is well seen in several ways. Thus the latest point of view toward focal infection is to the effect that since focal infection does not always produce proliferation of the synovial membrane it cannot have any immediate importance to the arthritic. Again, since systemic rest, from this point of view, does not alone arrest all cases of arthritis, it is alleged to be of no definitive value. Such an attitude constitutes loose thinking and cannot be condoned. Dispassionate reasoning dictates, for example, that attention should be given to the low metabolic rate found in a patient presenting rheumatoid disease, despite the fact that not all persons with rheumatoid disease present a low metabolic rate.

The chronic invalid is the subject of many disabilities, some of which are open to correction, others of which are inaccessible to any measures now available. Thus eroded cartilage cannot be replaced. Common sense again dictates, however, that those deviations which are open to correction, such as fatigue, edema, focal infection, should be regarded as integral parts of the problem and not dismissed as irrelevant because one feature of arthritis, say proliferation of the synovialis, is not specifically arrested thereby.

It is to be emphasized, however, that a patient may show marked improvement, amounting to full clinical relief, in the presence of an anemia which still persists and a sedimentation rate which remains elevated. This is not to be interpreted as evidence that anemia and an increased sedimentation are not to be regarded as important and constituting part of the picture. It is to be interpreted, however, as evidence that neither an increased sedimentation rate nor any other single factor, even articular lesions, can necessarily be regarded as a true criterion of the whole arthritic process. Incidentally, these considerations bring into relief the extent to which arthritic manifestations depend for their expression, in part at least, upon tissue edema. In some cases this condition may, indeed, seem almost to constitute the disease, so far as the patient's subjective and objective discomforts are concerned.

It has been well said that arthritis is a systemic disease with articular manifestations. It might be better, however, to say that patients ill with rheumatoid disease present a wide variety of symptoms which sometimes include articular disturbances. In this view the care of the patient with rheumatoid disease requires not the uniform application of a single measure to all, but rather the application to any patient of all measures which can in principle contribute to the correction of the various disturbances presented by arthritics as a group.

The field of arthritis still contains many therapeutic "defeatists" who, depending upon a few single agencies to correct the syndrome, experience frequent disappointment and come to believe that the

problem is intractable. Inquiry into such situations usually reveals that no real attempt has been made to pursue logically the physiologic leads available. William Penn once remarked, "Perhaps the worst part of this Vanity is its unteachableness. Tell it anything and it has known it long ago and outruns information and instruction." The arthritic patient is full of information for his medical adviser, but the adviser must have care lest he be "unteachable" and outrun instruction.

Conclusions. It is apparent that the widely held view is inadequate which regards the sole function of foodstuffs for the adult arthritic as limited to the provision of energy and regards all kinds of iso-caloric diets as equivalent for him. The proportion in which each dietary component is supplied is also important. In chronic and degenerative disease the proportions of the foodstuffs as well as the amounts should be given precise consideration.

Nutrition must thus be optimal not merely in respect to maintenance of a normal organism but also within the narrower necessities of the arthritic. The fact that arthritics may recover when the favorable influences of optimal nutrition, as above described, are not provided, in no way negates this truth. Arthritics may also recover in the presence of infections or without the benefits of physical therapy, but recovery may be significantly expedited if advantage be taken of all favorable influences which can be brought to bear by appropriate coördination of them. The various deviations from normal presented by arthritics as a group should be regarded as integral parts of the clinical problem. Certainly to deny to the struggling arthritic correction of these several deviations because the whole story is not understood and because no one of the factors involved alone induces or "cures" the disease, is to fail to see the problem in the light of all that modern medicine affords.

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THE WATERHOUSE–FRIDERICHSEN SYNDROME.

ACUTE BILATERAL SUPRARENAL HEMORRHAGE.

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No more dramatic episode may face the pediatrician than the evolution of the so-called Waterhouse-Friderichsen syndrome. Since Völcker[18] first recorded a death within 24 hours of onset of illness in a 2-year-old infant, with necropsy findings of purpura and bilateral adrenal apoplexy, until this present report, a search of the literature has revealed but 89 cases. Since it is our opinion that this is a clinical entity too often neglected, we wish to reëmphasize the salient features and record 7 cases of our own, in the confident expectation that others will be spurred to note their observations, and perhaps initiate appropriate treatment which might be life-saving.

Blaher and Bailey[3] were apparently the first to record a group of cases which fitted the clinical picture which we recognize today; in 1901, they suggested that the etiology was a fulminating hemorrhagic smallpox and definitely inclined to the theory that it was "probably a blood poisoning of some form." In the same year, Graham Little[11] collected 11 similar cases and noted that the bacteriology was negative. In 1911, R. Waterhouse[19] presented a case of his own and collected 15 from the literature; he claimed a distinctive clinical picture which had not heretofore been recognized, but added nothing as to the etiology. Then for the first time, in 1916, MacLagan and Cooke[13] wrote of 2 cases of fulminating cerebrospinal fever with recovery of the meningococcus. When Friderichsen[8] summarized the literature in 1918 the syndrome we now recognize assumed its title. Excellent contributions to the literature have since been made by various authors—Aegerter,[1] in 1936, Sacks,[17] in 1937, and Kunstadter,[10] in 1939, reviewed the published reports, the latter author collecting 74 cases. Since that publication approximately 14 cases have been added; the addition of our 7 cases brings the total to 96.

Symptoms. Ninety per cent of the cases occur in children varying from 6 months to 9 years; Aegerter[1] states that 70% of the patients have been under 2 years. In our series, the eldest was 6 years,

the youngest 6 months and the average 3.37 years; according to sex and race, there were 5 males and 2 females and 5 white and 2 colored infants. The typical anamnesis relates of a previously healthy child, who having gone peacefully to sleep, awakens with a cry. The signs and symptoms that follow are not characteristic but gradually crystallize into an unmistakable pattern. Headache, malaise, anorexia, slight elevation of temperature may be the only signals of the impending catastrophe. Vomiting is an early feature, but is not persistent; abdominal pain and diarrhea are of variable occurrence. Central nervous system signs are not prominent until later. Likewise in our experience, the birth, developmental, and familial histories were non-contributory. The onset was sudden, accompanied in 5 cases by vomiting and variously involving headache, abdominal pain, fever, cyanosis, and convulsions as the chief complaint. We wish to draw attention to the history of 1 of our patients whose mother stated that "the rash was not present when the child left the house for the hospital." This diagnostic statement was first recorded by Blaher and Bailey[3] and later by Brown.[4]

Within 8 to 12 hours of the onset a striking cyanosis occurs, this being generally the first sign which brings the patient to the hospital. Sacks[17] notes that the cyanosis was present in 46% of the cases and varied from a deep blue involving both the lips and nails to an alternation of cyanosis with pallor, which occurred in 2 cases; Magnusson[14] states that this phenomenon when present in an acutely ill child is diagnostic. Following the cyanosis, petechial mottling of any part of the body appears; the appearance is characteristic and as the hemorrhages involve more and more of the skin area, the body surface assumes the postmortem lividity described by Aegerter.[1] Weak irregular heart action and peripheral collapse are more likely to supervene as the condition of the patient becomes more critical. Concomitantly with the appearance of the rash, or shortly following, the individual becomes moribund or stuporous and this condition persists until death occurs.

Initial examination reveals an acutely ill child, the respirations and pulse always being rapid. The temperature is characteristically septic and may vary from 98° to 108° F., but in the majority of instances is above 103° F.

An examination of the temperature charts of our patients reveals the following pertinent data:

	Temperature.	*Pulse.*	*Respiration.*
High	107.0	156.0	48.0
Low	99.0	136.0	40.0
Average	104.2	144.4	42.5

The extremities are generally cold, the body hot, and this peripheral circulatory failure has been said not to occur until the adrenal damage has taken place. The heart and lungs reveal little beside a moderate number of basal moist râles. The abdomen is negative.

TABLE 1.—CLINICAL DATA IN 7 CASES OF WATERHOUSE-FRIDERICHSEN SYNDROME.

Case.	Age (yrs.). Sex. Race.	Duration of illness.	Admitting diagnosis.	Treatment.	History.	Physical examination.	Blood examinations.
J. C. 11/29/35	2½ W. F.	15 hrs. 5 mins.	Tonsillitis Possible: (1) Meningitis (2) Purpura hemorrhagica	Oxygen Amytal Lumbar puncture Caffeine Adrenaline	Awoke at night and vomited; 5 hrs. later purpura appeared, and 4 hrs. following, convulsions occurred	T. 105° F.; P. 140; R. 40 Good nutrition; acutely ill; neck rigid; naso-pharyngitis; generalized purpura	W.B.C. 12,000; 52% neutrophils
D. M. 12/9/35	3 W. M.	48 hrs.	(1) Purpura (2) Septicemia (3) Meningitis	Oxygen Caffeine Adrenaline Coramine	Physician stated that a convulsion occurred 40-48 hrs. prior to admission	T. 99.4° F. Good nutrition; moribund; pharyngitis; heart action irregular, poor quality; generalized purpura	
E. R. 3/22/36	6 C. M.	17 hrs. 25 mins.	Not made	Lumbar puncture Coramine Adrenaline Transfusion	Headache, vomiting, fever, delirium; rash not present when patient left home for hospital	T. 106° F. Good nutrition; acutely ill; naso-pharyngitis; ptosis of left eyelid; petechiæ over face; spinal fluid—suggestion of cloudiness	
R. S. H. 3/25/36	1 W. M.	12 hrs. 30 mins.	(1) Blood dyscrasia (2) Epidemic meningitis (3) Resolving pneumonia	Oxygen Adrenaline Coramine Calcium gluconate Transfusion	Vomited, 6 hrs. later purpuric hemorrhages appeared on face, later over legs	T. 104.6° F Fair nutrition; acutely ill, cervical and axillary adenopathy; naso-pharyngitis; lungs: left, crepitant and subcrepitant râles; liver palpable; generalized purpura; spinal fluid clear	Hemoglobin 8.79 gm.; R.B.C. 4,550,000/c.mm.; W.B.C. 12,200/c.mm.; 38% neutrophils; platelets 110,000/c.mm.
L. C. 5/16/36	5 C. M.	16 hrs. 40 mins.	Waterhouse-Friderichsen syndrome	Adrenaline Eschatin Meningococcus antitoxin Transfusion	Coryza for 1 wk.; abdominal pain, vomiting and chills	T. 103.6° F.; P. 140; R. 43 Fair nutrition; acutely ill; naso-pharyngitis; hyperesthesia, positive Kernig and Brudzinski; purpura coalescing	Hemoglobin 11.48 gm.; R.B.C. 5,440,000/c.mm.; W.B.C. 23,500/c.mm.; 76% neutrophils; platelets 330,000/c.mm.; bleeding time 3½ mins.; coagulation time 3½ mins.
R. S. 8/23/37	5½	14 hrs. 25 mins.	Undetermined	Oxygen Coramine	Pain in chest and vomiting, 6 hrs. later became comatose	T. 107° F.; P. 156 Comatose; pharyngitis; heart action weak; extremities cold, body hot	Hemoglobin 12.92 gm.; R.B.C. 4,260,000/c.mm.; W.B.C. 7800/c.mm.; 42% neutrophils; CO_2 combining power 12 vol. %; N.P.N. 52 mg. per 100 cc.; sugar 76 mg. per 100 cc.
H. P. 1/4/38	½ W. M.	13 hrs. 30 mins.	Meningococcal septicemia Bronchopneumonia Septicemia	Oxygen	Rhinopharyngitis for 2 wks.; fever and cyanosis this A.M.	T. 104° F. Good nutrition, acutely ill; naso-pharyngitis; generalized purpura	

Neurologic examination gives variable results. Less common findings, as listed by Aegerter,[1] include muscle flaccidity, tremor, chills, strabismus, convulsions and rigidity of the abdominal muscles. Cyanosis and purpuric hemorrhages were present in all of our cases. Physical examination revealed variable findings, although the presence of an injected pharynx and hypertrophied reddened tonsils were noted in all.

Laboratory examination may not be helpful. Leukocytosis should occur but the majority of the patients expire before adequate examination can be performed. Lumbar puncture is of value in direct relation to the progress of the condition; abnormal findings are generally present shortly before death. Smear and culture of purpuric skin areas, as suggested by McLean and Caffey[12] will, in our opinion, prove of value in a majority of the cases. This procedure has not been used extensively in the syndrome under discussion. Bamatter,[2] who states that low blood sugar values are pathognomonic of this disease condition, nevertheless concludes that the converse may be true as evidenced in his own case report. Magnusson[14] has also reported low blood and spinal fluid glucose values and feels that, in other conditions, even shortly before death, the blood sugar is maintained at a normal value.

The average white blood cell count which we obtained was 13,875, of which 57% were neutrophils. The thrombocytes were estimated in only 2 cases, averaging 220,000. In 1 case, blood findings included sugar 76 mg. per 100 cc., non-protein nitrogen 52 mg. per 100 cc., and carbon dioxide combining power 12 vol. %. The spinal fluid varied in cellular content from 6 to 202 cells and averaged 82 cells in the five fluids which were examined before death; the neutrophils averaged 64%.

Pathology. Bilateral adrenal hemorrhage has occurred in 95% of the reported cases, according to Aegerter.[1] These findings vary from petechial hemorrhages to bleeding, converting the organ into a "blood cyst." When the bleeding was mild in degree it was generally stated that the medulla was more involved than the cortex, and that the right adrenal was more often damaged than the left. Various theories have been advanced as to the causation. Among the possibilities suggested by Firor[7] are: 1, venous thrombosis; 2, toxins causing an increased permeability with rupture of the venous walls; probably bacterial embolism is a factor. Why the adrenals are more vulnerable than other tissues cannot be answered but possibly the biologic action of the gland or a relative increase in blood flow through these veins may be the answer. We feel that the combination of venous thrombosis and an increased permeability due to toxins from virulent organisms lodged in the vessels may explain the majority of cases. Sacks[17] stated that the involvement of the skin and adrenal medulla, both of similar ectodermal origin, is an evidence of the ectodermal tropism of the meningococcus.

TABLE 2.—AUTOPSY FINDINGS IN 7 CASES OF WATERHOUSE-FRIDERICHSEN SYNDROME.

Case.	Thymus (gm.).	Brain.	Mediastinal and bronchial nodes.	Spleen (gm.).	Mesenteric nodes.	Adrenals.	Spinal fluid.	Heart's blood culture.
J. C.	38.0	Not examined	Reddened and enlarged	Normal	Reddened and not enlarged	Right 5 gm., left 9.5 gm.; dark mahogany, due to hemorrhage	Cell count 6; neutrophils 50%; globulin increased; sugar normal; culture *Neisseria intracellularis*	*Neisseria intracellularis*
D. M.	39.0	Edematous and soft; extensive greenish-yellow exudate	No note	200.0 (Normal 37.0)	Not enlarged	Both markedly hemorrhagic	Cell count 1420; neutrophils 50%; globulin increased; sugar decreased; culture *Hemophilus influenzæ*, postmortem	*Hemophilus influenzæ*
E. R.	27.0 Petechial hemorr.	Some swelling; no definite exudate	Reddened and prominent	Normal	Red and prominent	Both markedly hemorrhagic	Cell count 202; neutrophils 98%; culture *Neisseria intracellularis* postmortem	*Neisseria intracellularis*
R. S. H.	28.5 Reddened	Meninges congested; convolutions moderately flattened	Prominent due to marked congestion	28.0	Prominent due to hyperplasia and occasional hemorrhage	Right 4 gm., left 4 gm.; hemorrhage scattered throughout medulla and cortex; periadrenal tissue has an edematous and grayish-mucoid appearance	Cell count 33; neutrophils 77%; culture *Neisseria intracellularis*	*Neisseria intracellularis*
L. C.	18.0	Meninges show a moderate hyperemia; convolutions moderately flattened	Hyperplastic and enlarged	Slightly larger than normal; follicles prominent	Hyperplastic	Right 4 gm., left 4 gm.; right is dusky red injected, no gross hemorrhage; left moderate hemorrhage into cortex	Cell count 87; neutrophils 75%; globulin increased; sugar normal; smear and culture *Neisseria intracellularis*	*Neisseria intracellularis*
R. S.	41.0	Increase in cerebrospinal fluid as indicated by the edematous appearance of the pia-arachnoid	No note	63.0 (Normal 52.0)	Slightly enlarged	Right, periadrenal edema and hemorrhage into the organ; left, considerable hemorrhage	Cell count 293; neutrophils 62%; culture *Neisseria flava II*, postmortem	*Neisseria flava II* *Alcaligenes fæcalis*
H. P.	23.2 Petechial hemorr.	Moderately edematous; slight exudate on surface	Enlarged, hemorrhagic and soft	37.5 (Normal 17.0)	Slightly enlarged	Right, not weighed; left, 4.5 gm.; deep maroon due to hemorrhage, infiltrated throughout	Cell count 986; neutrophils 8%; culture *Hemophilus influenzæ* postmortem	*Hemophilus influenzæ*

Rabinowitz[16] and Bamatter[2] have drawn attention to the prominence of the thymolymphatic system in those who succumb to this infection. In our 7 cases the thymus varied in weight from 18 to 41 gm., averaging 30.7 gm., displaying petechial hemorrhages in 4 cases. In 4 patients the bronchial and mediastinal nodes were enlarged and hemorrhagic; in 6 the prominence and redness of the mesenteric lymph nodes was notable. The spleen was definitely enlarged in 3 cases. The relation of these findings to the rapid exitus leads to interesting speculative possibilities. That these prominent lymphoid structures may regress rapidly is a known fact; whether they may attain a similar prominence from a former normal state is an unknown, but interesting possibility. Whether the controversial status thymolymphaticus enters into this picture may excite some comment, but the definite relation of these findings to this disease condition remains unknown.

Postmortem findings in the other viscera are not remarkable, varying widely in different cases.

Etiology. Although numerous investigators have suggested that the meningococcus may be the sole cause of this syndrome, we wish to point out that our experience does not lead to such a conclusion. In 2 of our cases the organism, as isolated from both the hearts' blood and cisternal fluid, proved to be the *Hemophilus influenzæ* and in another, *Neisseria flavus II* was present.

Although the isolation of organisms from these cases proved to be of great difficulty to early investigators, Dudgeon,[6] in 1904, found *Staph. aureus* in 1 case and pneumococcus in another. It seems quite possible that the pneumococcus represented the etiologic organism in that particular case. Both Mair[15] and Julianelle and Reimann[9] have reported on the ability of the pneumococcus to produce purpuric skin lesions and on the epithelial tropism of this organism.

Although the meningococcus is by far the most frequent offender, the only other organism obtained with any frequency being the *Strep. hemolyticus* (Snelling and Erb, quoted by Sacks[17]), it must be borne in mind that this organism does not represent the sole etiologic factor in all cases. It is our opinion that with proper technique and precautions the responsible organism will be recovered in the majority of cases.

Treatment. Since the diagnosis must be corroborated by postmortem observation, it is obviously difficult to evaluate the effect of adequate therapy. However, it is our belief that in the presence of a patient in whom a tentative diagnosis is ventured, treatment should be instituted immediately. According to the pathology, this should theoretically consist of: 1, measures to combat the invading organism; 2, measures to combat the suprarenal damage; and 3, supportive treatment.

We feel that the *Neisseria meningitidis* is responsible for the majority of cases and that the *Hemophilus influenzæ* may account

for the greater proportion of the remainder; consequently, when the invader is not immediately identified, it is logical to assume the presence of either of the two above-mentioned pathogens. In that case, antimeningococcus antitoxin should be administered by the intravenous route and anti-influenzal serum intramuscularly.

Although sulfanilamide has been favored at this writing by the majority of investigators, it is possible, judging from recent reports, that sulfapyridine will replace it as the drug of choice; we therefore recommend its administration in adequate dosage, first intravenously in the form of the soluble sodium salt, later *per os*.

Both epinephrin and cortin or desoxycorticosterone should be supplied in the desperate effort to maintain the somatic equilibrium; sodium chloride should also be given. Intravenous glucose and blood transfusion are also necessary therapeutic adjuncts.

Due to the fulminant character of this malignant infection, an immediate supply of the above-mentioned defense factors is an essential if we hope to reduce the present 100% mortality. Carey[5] has recently reported a case of recovery in a 27-year-old white female, although therapy was not instituted for approximately 21 hours after the onset of symptoms; his success in an apparent case of this nature is encouraging.

Comment. Attention is drawn to the ease of diagnosis of the Waterhouse-Friderichsen syndrome if the condition is kept in mind. In the presence of a previously well, but critically ill child, without localizing signs, this disease complex must be considered. The clinical course will corroborate or disprove the diagnosis; in the meantime, laboratory facilities may enable this clinical diagnosis to be confirmed and appropriate therapy instituted.

With other investigators, we strongly urge that future studies endeavor to correlate the known thymolymphatic prominence of the individuals who succumb to this disease and its possible relationship to the peculiar pathogenesis.

It is interesting to note that the statistics of this hospital reveal that influenzal meningitis occurs as frequently as meningococcic meningitis if epidemic periods be eliminated. Thus, it would seem that future investigators may find *Hemophilus influenzæ* in a similar proportion of this syndrome as an etiologic agent.

Speculative, also, is the fact that of the total 89 cases reported thus far, 30 had been published by 1904. Whether the following dearth of similar reports was due to a scarcity of such cases, decrease in virulence, or lack of recognition is not known; however, the latter possibility seems to be the most likely.

Conclusion. Seven cases of acute bilateral suprarenal hemorrhage are reported.

The bacteriologic offender was identified in each instance; four infections were attributed to *Neisseria meningitidis*, two to *Hemophilus influenzæ* and one to *Neisseria flavus II*.

We feel that the syndrome occurs more frequently than is now

estimated. In the presence of an illness of apoplectic onset in a previously well infant the appearance of alternate pallor and cyanosis or purpura, peripheral collapse, or hypoglycemia may well suggest the diagnosis.

It is felt that the prominence of the thymolymphatic apparatus in victims of this infection is worthy of investigation.

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THE CEREBROSPINAL FLUID TOTAL PROTEIN IN THE ALCOHOLIC PSYCHOPATHIES.

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This study resulted from the observation that the cerebrospinal fluid total protein was abnormally elevated in several patients suffering from such alcoholic psychopathies as delirium tremens and Korsakow's psychosis. These findings were rechecked, and after ruling out other possible contributory factors, it was felt that further investigation was warranted in view of the significance of elevated total proteins in other conditions affecting the central nervous system. A review of the rather meager literature on this problem revealed some suggestive but generally non-confirmatory material. Bargues and Berthon[1] reviewed several series of cases. They cite Villaret who reported increased cerebrospinal fluid albumin in only

2 of 12 cases of delirium tremens. This work was done in 1910, 10 years before the development of more accurate methods for quantitative determination of total proteins. They include Abadie and Pauly's series of 33 cases of chronic alcoholism with mental complications, in which only 39% showed a definite "hyperalbumose." They also report a series studied by Mele and Truck in which 40% of cases showed a slightly increased protein. Courtois and Picard[3] examined the cerebrospinal fluid total protein in 87 cases of simple alcoholism, 9 cases of alcoholism with "épilepsie toxique" and 4 cases of Korsakow's psychosis. In this series only 1 case in the second group was above 40 mg. per 100 cc. Eight cases in the first group had values over 30 mg. per 100 cc. while none of the Korsakow psychoses were at all normal. Neel[13] found above normal values in 142 of 209 cases of chronic alcoholism. Unfortunately the percentage of mental complications was not noted.

The above material did not seem to be adequate both because of the paucity of cases and the questionable validity of the procedures employed. The following investigation was then undertaken in an attempt to demonstrate whether or not the cerebrospinal fluid total proteins in the alcoholic psychopathies were increased consistently enough to be statistically significant.

Method. The present series consisted of 102 consecutive cases of alcoholism admitted to the Psychiatric Division of the Albany Hospital. The diagnosis of alcoholism, with or without psychopathy, was made at all times in concurrence with the opinion of the psychiatric staff members. Lumbar puncture was done within 48 hours of admission. Total proteins were determined* by the nephelometric method of Dennis and Ayer[5]. Both leukocyte and erythrocyte counts were done on the same specimen within 2 hours after puncture. Cerebrospinal fluids containing erythrocytes were not included in the cases statistically studied as it was found that as few as 10 to 30 erythrocytes per c.mm. produced erroneous protein values and frequently gave a positive Pandy reaction. Cases which subsequently revealed concomitant central nervous system disease such as neurosyphilis, multiple sclerosis, cerebral concussion, idiopathic epilepsy or psychosis with cerebral arteriosclerosis were omitted.

Results. Table 1 presents the data on cases with cerebrospinal fluid total proteins of 40 mg. per 100 cc. and below. Table 2 does likewise with values above 40 mg. per 100 cc. Forty-two cases in the first category gave an average total protein of 31.9 mg. per 100 cc., with values ranging from 14.1 to 40 mg. per 100 cc. Sixty cases comprising the second group averaged 58.6 mg. per 100 cc. of total protein with values ranging from 40.3 to 118 mg. per 100 cc. Of the 60 cases having total proteins of over 40 mg. per 100 cc., 43 cases (71.6%) had definite direct or indirect central nervous system complications of alcoholism. Of the 42 cases with values of 40 mg. per 100 cc. and below, 10 cases (24.2%) had central nervous system complications. Table 3 gives an analysis of the

* Total protein determinations were made by the Department of Biochemistry of the Albany Medical College.

different alcoholic psychopathies encountered, totalling 53 cases with an average total protein of 52.8 mg. per 100 cc. The 49 cases of uncomplicated alcoholism averaged 37.7 mg. per 100 cc. Cerebrospinal fluid cytology was not significant, only 8 cases having leukocyte counts over 10 cells per c.mm.

TABLE 1.—SPINAL FLUIDS WITH TOTAL PROTEINS OF 40 MG. PER 100 CC. AND BELOW IN ALCOHOLICS.

Patient.	Age.	Sex.	Duration of alcoholism.	Associated mental state	Total protein, mg. per 100 cc.
1. A. G.	40	F	3–5 yrs.	?Paranoid schizophrenia	36.7
2. J. L.	42	M	10–15 yrs.	None*	30.4
3. R. W.	51	M	"Social drinking"	?Paranoid reaction	32.8
4. F. W.	29	M	3–4 mos.	Polyneuritis	30.0
5. R. P.	56	M	15–20 yrs.	None	35.0
6. F. C.	52	M	15–20 "	Mild CO poisoning	35.7
7. W. Mc.	44	M	10 "	None	39.2
8. M. K.	42	M	10 "	None	33.7
9. A. W.	48	M	5 "	None	21.5
10. W. H.	46	M	20 "	?Lateral sclerosis	35.7
11. A. S.	35	M	3 "	None	22.5
12. E. L.	45	M	20 "	None	33.8
13. E. K.	40	F	3 "	None	24.5
14. W. G.	52	M	20 "	None	35.7
15. E. G.	29	F	4 "	None	32.0
16. F. T.	47	M	15–20 "	Polyneuritis	32.4
17. L. H.	28	M	6 "	Catatonic schizophrenia	36.0
18. F. G.	34	M	"Social drinking"	None	31.2
19. W. W.	27	M	"Social drinking"	None	29.7
20. H. C.	41	M	10–15 yrs.	Delirium tremens	23.8
21. J. C.	37	M	6 "	None	39.0
22. J. Mc.	42	M	25 "	Mild confusion	22.0
23. C. R.	41	M	3 "	Delirium tremens	30.8
24. J. P.	42	M	15 "	None	26.0
25. E. R.	40	F	10 "	None	23.8
26. L. D.	38	F	5 "	Overactive at times	14.1
27. J. B.	42	M	? "	None	32.0
28. J. B.	33	M	? "	None	39.2
29. F. H.	38	M	? "	Transitory confusion	27.4
30. W. N.	43	M	4 "	Convulsive, hypertension	36.0
31. W. M.	46	M	20 "	Epileptiform seizures	25.0
32. H. H.	24	F	4–5 "	Acute hallucinosis	29.4
33. E. S.	38	M	8–10 "	Slight tremor	38.1
34. C. W.	39	M	5 "	None	31.6
35. K. Mc.	31	M	5 "	Acute hallucinosis	38.1
36. A. G.	21	M	8–10 mos.	None	31.2
37. F. Mc.	40	M	10 yrs.	Depressive state	39.6
38. G. M.	52	M	3–5 "	Epileptiform seizures	40.0
39. W. F.	33	M	6 mos.	None	28.7
40. W. G.	39	M	7–8 yrs.	None	27.0
41. F. G.	48	M	10–15 "	Paranoid reaction	33.0
42. H. B.	34	M	5–6 "	None	55.5

* "None" indicates acute alcoholic intoxication limited to 48 hours.

Discussion. The findings indicate a definite tendency for the cerebrospinal fluid total proteins to be pathologically increased in the alcoholic psychopathies. The statistical support for this contention is obvious even after allowance is made for the fact that the method used has a possible technical error of 10%. The Dennis-Ayer method used in this work has been generally accepted and regarded as quite reliable. Brown, Gildea and Man[2] compared this procedure with two Kjeldahl methods and found agreement within 12 mg. per 100 cc., the Dennis-Ayer method always giving the lowest values.

Total protein values above 40 mg. per 100 cc. were regarded as indicating pathologic increase. That this somewhat arbitrarily chosen dividing line is not too low is supported by the work of numer-

TABLE 2.—SPINAL FLUIDS WITH TOTAL PROTEINS ABOVE 40 MG. PER 100 CC. IN ALCOHOLICS.

Patient.	Age.	Sex.	Duration of alcoholism, (yrs.).	Associated mental state.	Total protein, mg. per 100 cc.
1. C. W.	49	F	20	Dipsomania	48.2
2. K. F.	41	M	10–15	Delirium tremens	55.5
3. E. S.	41	F	10–15	Atypical Korsakow's psychosis	40.3
4. J. A.	67	M	20	Hallucinations, delusions	45.0
5. C. F.	66	F	20	?cerebral arteriosclerosis	46.5
6. C. C.	55	M	20	Depressed state	61.5
7. B. T.	65	M	20	Convulsions	73.0
8. F. H.	45	M	2	Bilateral optic neuritis	44.0
9. N. Mc.	39	M	10(?)	Delirium tremens	52.0
10. P. Mc.	47	M	20	Delirium tremens	63.5
11. P. D.	31	M	6	Depressed state	68.0
12. O. P.	51	M	25	Confused, disoriented state	72.7
13. G. H.	63	M	20	Delirium tremens	66.6
14. F. O'H.	55	M	25	Paranoid reaction	72.7
15. T. H.	66	M	25	Confused state	49.4
16. J. S.	33	M	3–4	Depressed state	53.3
17. T. M.	53	M	2–3	Delirium tremens	50.6
18. G. J.	50	M	20	Manic delirium	50.0
19. W. Mc.	50	M	10–15	Convulsive state	61.5
20. J. S.	38	M	12	Delirium tremens	48.2
21. R. B.	41	M	18	Delirium tremens, polyneuritis	95.0
22. B. K.	34	M	10–15	None (formerly had neurosyphilis)	71.4
23. J. W.	52	M	20	Comatose state (20 hours)	62.5
24. C. P.	50	M	10–20	None	45.0
25. H. W.	48	M	30	Confusion, tremors–polyneuritis	50.0
26. R. J.	37	F	16	Delirium tremens	45.5
27. E. D.	35	M	12	None	45.5
28. H. T.	56	M	30	Delirium tremens	44.4
29. B. S.	56	F	25	Toxic psychosis ?bromidism	53.3
30. J. W.	52	M	20	Comatose state (24 hours)	62.5
31. M. Mc.	51	F	10	Depressed state ?menopausal syndrome	46.0
32. R. L.	39	M	7	Manic delirium	46.5
33. M. G.	54	M	20	Paranoid reaction	64.5
34. L. C.	52	M	20	Delirium tremens	40.4
35. J. M.	25	M	5	None	48.7
36. J. Z.	54	M	30	Delirium tremens	62.5
37. M. W.	37	F	10	Polyneuritis–overactivity	50.0
38. E. L.	31	M	5	Comatose state (10 hours)	52.0
39. J. G.	50	M	20	Korsakow's psychosis	47.6
40. J. H	39	M	10–15	Acute hallucinosis	48.7
41. M Mc.	32	M	2½	Depressed, anxiety state	72.7
42. A. R.	30	M	5	Convulsive state	64.5
43. H. W.	48	M	15–20	None	45.5
44. B. L.	38	M	13	Psychopathic personality	50.0
45. J. D.	42	M	15	Reactive depression	59.0
46. E. W.	38	M	10	Reactive depression	50.0
47. M. G.	42	F	10	Paranoid reaction	49.4
48. J. H.	38	M	15–20	Delirium tremens	118.0
49. J. F.	39	M	5–10(?)	None ?head trauma	59.4
50. M. L.	35	F	10	Delirium tremens	55.5
51. W. Mc.	31	M	10	Manic delirium	57.0
52. J. S.	40	M	15	Korsakow's psychosis	46.0
53. A. K.	42	M	10–15	Comatose state (15 hours)	65.5
54. J. O.	49	M	10–15	Korsakow's psychosis*	80.0
55. J. K.	45	M	20	Delirium tremens	74.0
56. W. W.	39	M	10–15	Epileptiform seizures	42.1
57. P. K.	46	M	20	Convulsive state (3 years)	75.0
58. E. S.	45	M	15–20	Delirium tremens	75.5
59. G. M.	62	M	15–20	Korsakow's psychosis*	106.0
60. B. M.	39	M	10–15	Korsakow's psychosis	69.0

* Memory loss, confabulation, disorientation present but polyneuritis absent.

ous investigators. Kafka,[9] using both Kjeldahl and Esbach techniques, found average values in normals to be 24 mg. per 100 cc. Phillips[16] (method not stated) offers normal values ranging from 20 to 40 mg. per 100 cc. Schube[17] prefers to consider normal range between 0 and 39.99 mg. per 100 cc. He quotes 22 writers employing different methods, 18 of whom found normal values definitely less than 40 mg. per 100 cc., 3 observed normal range from 17 to 50 mg. per 100 cc., while 1 felt that the diversity of normal values was much greater, namely, 35 to 100 mg. per 100 cc.

TABLE 3.—ANALYSIS OF DATA.

Alcoholic psychopathies.	Cases with total protein over 40 mg. per 100 cc.	Cases with total proteins of 40 mg. per 100 cc. and below.	Average total proteins, mg. per 100 cc.
1. Acute hallucinosis	2	2	42.9
2. Delirium tremens	15	2	58.3
3. Confusion with polyneuritis	3*	2†	41.3
4. Paranoid reaction	3	3	48.2
5. Korsakow's psychosis	6	0	55.6
6. Convulsive states	5	0	64.7
7. Manic delirium (without tremor)	5	1	51.1
8. Comatose, stuporous states	4	0	60.6
Totals	43	10	52.8‡

* One case was predominantly an optic neuritis.
† These 2 cases presented very little psychopathology.
‡ Average total protein in all cases of central nervous system complications of alcoholism.

Assuming then that the results do show an abnormal increase of cerebrospinal fluid total protein in the alcoholic psychopathies, what does this signify? Before attempting to answer this question it is necessary to clarify our concepts with respect to several points, namely, the origin of normal cerebrospinal fluid total protein, the significance of so-called pathologic values of total protein in other central nervous system diseases, the relationship of total protein to the permeability of the hemato-encephalic barrier, and finally, the significance of barrier permeability in lesions of the central nervous system. Complete knowledge on these several aspects of the problem is lacking, but some work has been done which offers suggestive leads for further study.

Authorities[8] state that under normal conditions blood plasma proteins do not penetrate the semipermeable membrane or hemato-encephalic barrier which separates the cerebrospinal fluid system from the blood stream. It is felt that the small amount of protein normally present is derived from the usual catabolism of the tissues of the central nervous system, although nothing seems to be known about the mechanism which prevents this material from eventually accumulating, provided of course that the original assumption is accurate. In pathologic conditions the protein is frequently abnormally elevated. Here, too, the source of protein increment is as yet an open question. Malamud, Miller and Mullins[12] rest the

matter in a choice between a hematogenic or a central nervous system destructive process. Schube[17] expresses the same viewpoint, adding that the hematogenic mechanism may be a direct transudation through dilated meningeal vessels. Thompson *et al.*[19] point out that cerebrospinal fluid protein is high in myxedema and questions the possible relationship of this finding both to the storage of nitrogenous substances and the frequent albuminuria which are present in myxedema. This observation favors the hematogenic theory. Deane[4] states that generalized increased intracranial pressure *per se* such as occurs in internal hydrocephalus does not increase the protein, but notes that the increased protein frequently found in intracranial tumors is caused by local compression of relatively non-anastomotic venous channels draining the choroid plexuses, especially in the lateral and third ventricles. He regards the choroid plexuses as the sites whence at least the major quantity of protein gains access into the cerebrospinal fluid in normal individuals and in cases of intracranial tumors.

It is known that increased protein in certain central nervous system diseases (neurosyphilis, meningitis, encephalitis) is frequently a crude indicator of the extent of the disease process, progress in the condition often being paralleled by the protein curve. On the other hand, this relationship does not hold in a number of other conditions such as paralysis agitans, multiple sclerosis, or idiopathic epilepsy. In epilepsy, Patterson and Levi[15] studied the proteins in 50 cases and found values unchanging and consistently under 30 mg. per 100 cc. The writer has found in an unpublished study of a series of organic psychoses of the senium that, although the cerebrospinal fluid protein was frequently elevated, repeated punctures done on subsequent occasions when the patients were improved, unchanged or worse failed to show a sufficiently significantly positive correlation between the protein curve and the clinical course. Apparently a consistent relationship between protein and all forms of central nervous system disease cannot be demonstrated. One gets the impression, however, that elevated protein points rather definitely to the presence of tissue lesions. Fremont-Smith *et al.*[6] sum up the situation with the statement that "values between 45 and 60 mg. per 100 cc. in the large majority of cases accompany central nervous system pathology."

Hemato-encephalic barrier permeability studies give additional meaning to the question of protein significance. Nicolajev,[14] Katzenelbogen[10] and Stern and Lokschina[18] among others point out that barrier permeability is increased in the majority of cases in which cerebrospinal fluid total protein is elevated. It is interesting to note that Malamud *et al.*[12] found that while the correlation between protein and barrier permeability quotient is not highly consistent as studied in manic-depressives, schizophrenics, psychoneurotics and a fourth group consisting of toxic and organic psychoses (cere-

bral arteriosclerosis and general paresis), the highest correlation occurred in the toxic-organic group.

The normal constancy of barrier permeability is regarded as the keystone in the defence which the central nervous system possesses against systemic invasion by disease processes. This barrier can be weakened by certain toxic agents and there is evidence to prove that one of these is alcohol. Gabriel, Palisa and Novotny[7] found in a series of cases of delirium tremens that the cerebrospinal fluid alcohol content was abnormally present in 45.3%. Furthermore they noted that the blood alcohol frequently returned to normal while the cerebrospinal fluid alcohol still remained high. Stern and Lokschina[18] tested barrier permeability on rabbits and guinea pigs subjected to acute and chronic alcohol poisoning. In acute brief intoxication experiments no change was found in the normal resistance to the passage of colloids. In chronic alcohol poisoning, however, a definite increased permeability for colloids was demonstrated. That alcohol also exerts a histotoxic action on nerve tissue itself is postulated by McFarland and Barach,[11] who claimed that the histotoxicity leads to a state of anoxia. They tested out this theory by giving severe alcoholic cases inhalations of a mixture consisting of 50% oxygen and 10% carbon dioxide. They found that both blood alcohol and blood lactic acid were drastically lowered with concomitant improvement in mental and motor behavior.

Conclusions. Evidence is presented to show that the alcoholic psychopathies in the great majority of instances are associated with elevated cerebrospinal fluid total protein. The literature strongly suggests that the alcoholic psychopathies are closely associated with a direct toxic effect of alcohol upon the central nervous system and that this action very frequently results in a pathologic increase of cerebrospinal fluid total protein. Part of this protein seems to be derived from the systemic circulation due to increased permeability of the hemato-encephalic barrier, while the remainder appears to result from pathologic central nervous system tissue catabolism. The normal protein values found in the 24.2% of cases in this series which showed alcoholic psychopathy cannot be accounted for except on the basis of individual variation in either nervous tissue or barrier permeability resistance.

Summary. 1. Cerebrospinal fluid total protein was determined on 102 consecutive cases of alcoholism.

2. Pathologic total protein values were found in 71.6% of all cases in which psychopathy was present.

3. The literature on the cerebrospinal fluid total protein in the alcoholic psychopathies was surveyed and the significance of the findings was discussed.

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USE OF ACETYL-BETA-METHYLCHOLINE CHLORIDE IONTOPHORESIS IN NON-ARTERIAL PERIPHERAL VASCULAR DISEASE.

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There are several favorable reports of the treatment of varicose ulcers,[4b,10] thrombophlebitis with and without ulceration,[9,11] and scleroderma[3] by iontophoresis with acetyl-β-methylcholine chloride. Kovacs first described the procedure and suggested the technique which has since been followed. Baker[1] recently had less favorable results in the treatment of a short series of patients having varicose ulcers, and more favorable results with older and simpler methods.

The present paper deals with the results of treating 42 patients by acetyl-β-methylcholine chloride iontophoresis in the Peripheral Vascular Clinic from October, 1937, to August, 1940. Kovacs'[4a] method was used, with the sole exception that 0.2% acetyl-β-methylcholine chloride* instead of 0.5% was used, since the difference in effect was indistinguishable clinically, and since experimental data bear out this clinical impression.[8] Any one patient received from 2 to 217 treatments: fewer than 10 treatments were considered an inadequate trial but all patients are reported (See Table 1). When the patient could tolerate it 20 to 30 milliamperes of current were used for 20 to 30 minutes, but the whole range was 5 to 30 milliamperes for 5 to 40 minutes.

Ten of the 42 patients had varicose ulcer, 6 post-thrombophlebitic ulcer, 11 chronic or subacute thrombophlebitis without ulcer, 6

* Merck & Co. kindly supplied the acetyl-β-methylcholine (Mecholyl) and special asbestos paper for iontophoresis.

TABLE 1.—SUMMARY OF CASES TREATED WITH ACETYL-β-METHYLCHOLINE IONTOPHORESIS.

No.	Sex.	Age.	Main vascular diseases.	Duration.	Previous treatment.	Previous results.	Iontophoresis.		Treatment.		Follow-up.		
							No.	Wks.	Supportive.	Results.	Time. Treatment.		Results.
			VARICOSE ULCER.										
1	F	49	Varicose veins, ulcer	17 yrs.*	Injections, gelatin boots	Healed, recurred	20	10	Elast. band. Injections	Painless, nearly healed	1 mo. injected vein		Healed
2	F	64	Varicose veins, ulcer	12 yrs.*	Gelatin boots	Steadily worse	49	22	Elast. band.	Less painful, little healing	5 mos. drained hematoma		Same
3	F	62	Varicose veins, ulcer, asthma	30 yrs.*	Skin graft, gelatin boots	Steadily worse	13	4	Saline soaks	Still painful, no healing, asthma	2 yrs. Gelatin boots		Better
4	F	51	Varicose veins, ulcer	14 yrs.*	Ligations, injections, boots	Steadily worse	45	23	Elast. band.	Less painful	2 yrs. Gelatin boots		Same
5	M	50	Varicose veins, ulcer	4 yrs.	0	Steadily worse	5	10	Elast. band.	Moderate improvement	2 yrs. Gelatin boots		Same
6	F	58	Varicose veins, ulcer	22 yrs.*	Gelatin boots	Slight healing	9	2½	0	0	No follow-up		
7	F	46	Varicose and phlebitic ulcers, decomp. heart	7 yrs.*	Bandages, boots	Stationary	62	53	Elast. band.	Temp. imp., less pain	2 yrs. Gelatin boots		Healed
8	M	70	Varicose eczema, hypertension	Many yrs.	Injections	Stationary	5	1½	Elast. band.	Temp. imp. less pain	No follow-up		
9	F	69	Varicose veins, phlebitic, painful ulcer site	7 yrs.	Ligations	Worse	5	1½	Elast. band.	Sl. subjective relief.	2 yrs. Gelatin boots		Healed
10	M	60	Varicose veins, phlebitic, varicose eczema	7 yrs.	Elastic bandages	Much worse	6	2	Elast. band.	Less pain, chills, discont.	2 yrs. Gelatin boots		Improved
			THROMBOPHLEBITIC ULCER.										
11	F	49	Thrombophlebitic ulcer	14 yrs.	Boots, sedatives	Steadily worse	60 (3 st. ages)	20	Elast. band. Insulin	Painless, almost healed	No follow-up		
12	F	40	Thrombophlebitic ulcer	1 mo.	Gelatin boots	Steadily worse	2	1½	Elast. band.	Less painful, too little R	No follow-up		
13	F	58	Thrombophlebitic ulcer	15 yrs.*	Multiple	Varying	21	7	Elast. stock.	Worse	1½ yrs. Linton oper.		Healed
14	F	28	Thrombophlebitic ulcer	3 yrs.*	Supports, injections	Varying	9	3	Elast. band.	Less tender, cleaner	6 mos. Gelatin boots		Same
15	F	33	Thrombophlebitic ulcer, healed, painful	11 yrs.*	Supports, injections	Stationary	18	6	Elast. band.	No improvement	9 mos. Linton oper.		Asymptomatic
16	M	31	Thrombophlebitic and varicose ulcer	5 yrs.	Elastic bandage	Worse	2	1	Elast. band.	No improvement	? mos. Saphenous liga.		Same
			OTHER ULCERS.										
17	F	51	Decubitus ulcer, nephrolithiasis	Weeks	Incision	Worse	4	1½	Back care	Sl. improvement	4 mos. Postop. care		Healed
18	M	59	Decubitus ulcer, splenomegaly	1 wk.	Back care	Sl. improved	6	1½	Back care	Healed ulcer	No follow-up		
19	F	12	Decubitus ulcer, transverse myelitis	6 wks.	Excision, back care	Steadily worse	15	4½	Back care	Steadily worse	1 mo. No therapy		Died of infect.

20	M	56	Ulcer in amputation stump, card. decomp.	2 mos.	0	Stationary	30	13	Rest	Ulcer healed	1 yr. Stayed healed	Died
21	F	22	Erythema induratum, ulcer	4 mos.	Boots, elastic bandage	Worse	12	4½	Elast. band.	Ulcer healed	No follow up.	
22	M	57	Erythema induratum, ulcer, card. decomp.	1 mo.	Bed rest	Worse	5	2½	Bed., card.	Not improved	1 mo. cardiac	Died
			THROMBOPHLEBITIS WITHOUT ULCER.									
23	F	42	Chronic thrombophlebitis	5 yrs.	Support, heat	Gradually worse	55 (2 st ages)	32	Elast. stock.	Completely relieved	1 yr. Elast. band.	Recurrence
24	F	53	Chronic thrombophlebitis	3 yrs.	Rest, elevation	Worse recently	12 (2 st ages)	4	Elast. band.	Completely relieved	1 yr. Arch supports	Still relieved
25	F	28	Subacute thrombophlebitis	4 mos.	0	Stationary	19	12	Elast. band.	Nearly comp. relief	No follow-up	
26	F	31	Chronic thrombophlebitis	1 yr.	0	Stationary	10	4½	0	Nearly comp. relief	No follow-up	
27	M	27	Chronic thrombophlebitis, edema	2 mos.	Supports, injections	Stationary	7	2½	Elast. band.	Nearly comp. relief; edema same	No follow-up	
28	F	27	Chronic thrombophlebitis	2 mos.	0	Stationary	18	7	Elast. band.	Nearly comp. relief; edema same	No follow-up	
29	F	32	Chronic thrombophlebitis, edema	2 yrs.	Supports, injections, diathermy	Stationary	8	2	Elast. stock.	Subjective imp.; edema same	6 mos. Elast. band.	Asympt., no edema
30	F	46	Chronic thrombophlebitis	1½ yrs.	Elastic stocking	Gradually worse	8	11	Elast. stock.	Subjective imp.	1 yr. Elast. stock.	About same
31	F	35	Chronic thrombophlebitis, thrombophlebitis, brawny edema, foot strain	8 yrs.	Elastic bandage	Stationary	4	2	Elast. band.	No relief, edema same	No follow-up	
32	F	39	Chronic thrombophlebitis, edema	7 yrs.	0	Stationary	27	13	Elast. stock.	Nearly comp. relief; edema same	No follow-up	
33	F	12	Chronic thrombophlebitis, brawny edema	29 mos.	Heat and massage	Stationary	25	10	....	No change in edema	4 mos. Bed rest	Softer
			SCLERODERMA.									
34	M	47	Scleroderma, generalized	3 yrs.	0	Steadily worse	110	40	Diathermy	Skin softer, joints imp.	2 yrs. Diathermy	About same
35	F	21	Scleroderma, generalized, calcinosis	3 yrs.	0	Steadily worse	217	132	0	No further progression	6 mos. Vasodilator drugs	Sl. imp.
36	F	36	Scleroderma, generalized, early	Incipient	0	Gradually worse	56	34	Phys. ther.	No change	1 yr. Arthritic	Sl. imp.
37	M	39	Scleroderma, generalized, fulminating	6 yrs.	Sympathectomy	Suddenly worse	21	6	None	Steadily worse	2 yrs. None	Steadily worse
38	M	32	Scleroderma, generalized	5 yrs.	Sympathectomy	Gradually worse	46	20	0	Skin softer, joints unimp.	No follow-up	
39	F	14	Scleroderma, localized (morphœa)	1 yr.	0	Steadily worse	36	14	0	Greatly improved	6 mos. Thyroid, etc.	Still imp.
			OTHER DISEASES.									
40	F	40	Acrocyanosis	30 yrs.	Thyroid	Gradually worse	12	4	0	No change	No follow-up	
41	F	33	Irritation of brachial plexus from scar	2 yrs.	0	Gradually worse	19	8	0	Less pain	4 mos. None	Symp. recurred
42	F	49	Raynaud's disease, fulminating type	6 wks.	Stopped smoking	Fulminating	8	2	Suction and pressure	Pain relieved	No follow-up	

* Recurrent ulcers prior to iontophoresis therapy.

ulcers of other origin, 6 scleroderma, and 3 had miscellaneous disorders. Patients with occlusive arterial disease were not chosen for treatment because the results of others have not been sufficiently favorable.[5] With one exception (Case 42, Table 1) patients with abnormal vasoconstriction were not chosen because the temporary vasodilatation afforded by acetyl-β-methylcholine chloride iontophoresis can be obtained by the simple means of heat.[8] In most instances iontophoresis therapy of varicose ulcer and thrombophlebitis was supplemented by the use of elastic bandages. Bed rest was used only when illness had kept a patient in bed before iontophoresis was started. Otherwise no other therapy was used during the periods of iontophoresis (exception see Table 1, Case 11). When ulcers were treated they were not covered by rubber dam as advised recently by Sokolov and Meyers.[11]

Varicose Ulcers. The initial experience with severe varicose ulcers was promising: after several treatments there was usually less pain, less odor, and some evidence of healing. Subsequently, however, there was little evidence of improvement, and not one of the ulcers healed solely as a result of iontophoresis therapy. A characteristic unfavorable response is shown in Figure 1. In 2 instances chills and fever resulted, probably from reactivation of infection from increased flow of blood through the veins. When the course of iontophoresis therapy was finished the patients were advised to have gelatin boots applied. Four of the 6 patients who had this done were further improved, 1 with healing; 2 were not improved. One other ulcer healed promptly after a vein which traversed the ulcer bed was injected with a sclerosing solution (details in Table 1).

Post-thrombophlebitic Ulcer. The results of iontophoresis therapy of ulcers developing as a consequence of previous thrombophlebitis were similar to the results in varicose ulcer. Only 1 of the 6 ulcers was markedly improved and success in that instance (Case 11, Table 1, Fig. 2*a*) may have come from diabetic therapy which was instituted shortly before the course of iontophoresis. A characteristic unfavorable response is shown in Figure 2*b* (Case 14). One of the unsuccessfully treated ulcers failed to benefit by high saphenous vein ligation and healed only after multiple ligation and section of communicating veins (Linton operation[6]). Another patient, with a painful area in the site of an old ulcer, was made symptom-free by a Linton operation (details in Table 1).

Other Ulcers. Three sacral bedsores, one ulcer in an edematous low-thigh amputation stump, one ulcer in a patient with erythema induratum and one in a patient with questionable erythema induratum and peripheral edema of cardiac origin were treated. One of the decubitus ulcers healed very promptly (Fig. 3, Case 18). The general health of this patient was improving, his activity in bed consequently was greater, and this may have contributed to the healing. Another patient's large decubitus ulcer would tolerate very little cur-

rent: it became steadily worse until the time of the patient's death 1 month later. The stump ulcer healed (Fig. 3, Case 20). Avoidance of the use of his artificial limb seemed to contribute. The ulcer

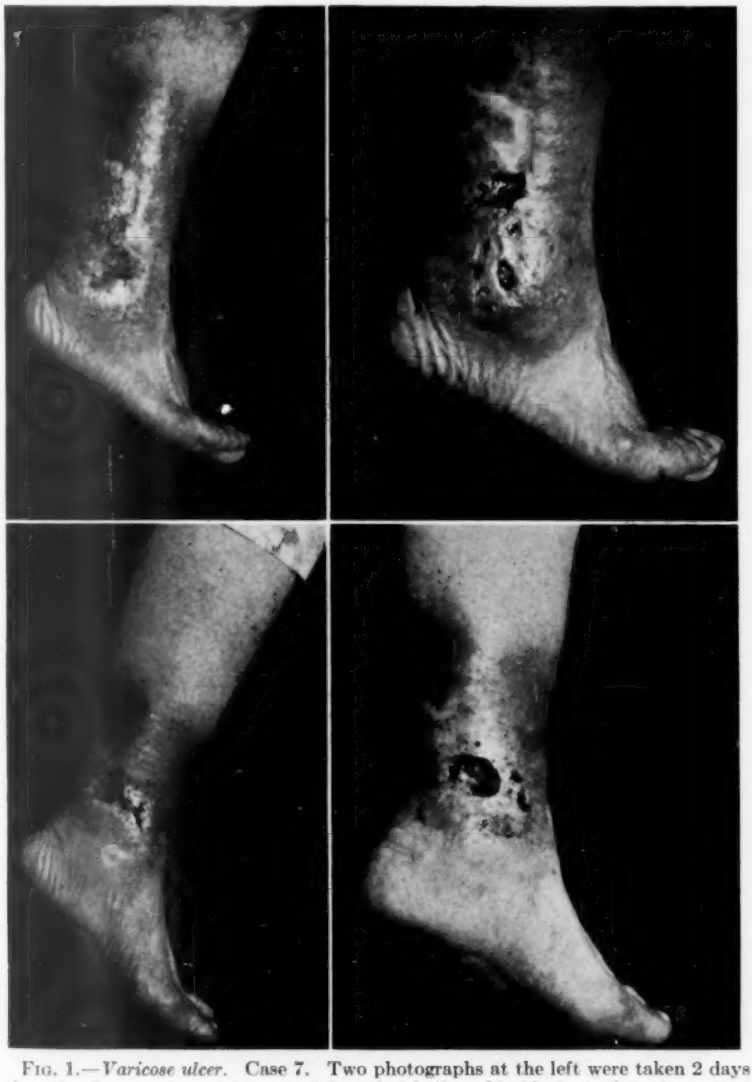

FIG. 1.—*Varicose ulcer.* Case 7. Two photographs at the left were taken 2 days after the first treatment by acetyl-β-methylcholine chloride iontophoresis; two at the right 1 month later (no improvement, ulcers less painful).

of 1 patient with erythema induratum healed (Fig. 3, Case 21); that of the other failed to heal and the patient died 1 month later of cardiac decompensation. When the third patient with decubitus

ulcer recovered from a severe urinary infection, the ulcer healed spontaneously (details in Table 1).

Thrombophlebitis without Ulcer. The results in the series of 11 patients with chronic thrombophlebitis without ulcer were fairly

FIG. 2*a*.—*Thrombophlebitic ulcers* Case 11. The 8 photographs on this and the following page of a single extensive ulcer in a diabetic patient receiving insulin and acetyl-β-methylcholine chloride iontophoresis. Photograph 1 was taken on the first day of treatment, the others 1 month, 1½, 2, 4, 13½ (11 months after discontinuance of iontophoresis), 14 (after resuming iontophoresis), and 15 months later.

good. Ten of the patients had pain, 1 probably from arch strain, and 9 the typical aching and heavy feeling aggravated by being in the vertical position, and worse in the afternoon. Eight of these 9 were more comfortable shortly after starting treatment, 2 completely

relieved, 4 nearly so. Two of the patients had excessively painful menstruation since the onset of the phlebitis; 1 for 4 months, 1 for 5 years. Pelvic vein thrombosis was the probable cause. Both were promptly relieved of this symptom. Six of the patients had some

degree of edema of the lower leg: in none was the edema influenced by treatment. Careful measurements were made during the therapy of an asymptomatic, simple, milk leg (Case 33). The size was unchanged by treatment. After a month of bed rest, elevation and elastic bandage, the circumference was lessened from 1 to 2 cm. and the leg made softer.

FIG. 2b.—*Thrombophlebitic ulcers.* Case 13. Two upper photographs: left view taken on first day of treatment, next one, right, 3 weeks later (worse). Case 14. Two lower photographs: left view taken on first day of iontophoresis, next 1 month later (improved).

These patients were followed too irregularly to secure a statistical appraisal of permanence of results. Two of the patients with heavy, tired feelings in the legs were relieved for 7 months, only to have the symptoms then return. In 1, prompt relief was again obtained

FIG. 3.—*Other ulcers.* Case 18, decubitus ulcer, upper two photographs: left taken on day first given iontophoresis, right taken 12 days later (healed). Case 21, ulcer, erythema induration, middle two photographs: left taken on day first given iontophoresis, right taken 1 month later (healed). Case 20, ulcer in amputation stump, lower two photographs: left taken on first day of iontophoresis, right taken 3 months later (healed).

after therapy. The other had developed varices for which high saphenous ligation was advised: she failed to comply. Improved footwear contributed to prolonged relief of 1 patient.

Scleroderma. Six patients with this disease were treated. In spite of prolonged therapy 1 continued to become worse, and 2 others were not measurably benefited (Fig. 4, Case 36). Two patients were moderately improved (Fig. 4, Case 35). One patient, with morphœa had a single thickened, hard, plaque of skin on the breast. This became almost normally soft within 2 weeks after starting therapy, and continued so with intermittent treatment for the 6 months in which the patient was followed.

Other Diseases. A patient with acrocyanosis and numb, stiff, blue hands, aggravated by cold, was entirely unimproved. A patient with brachial neuritis, which followed a thyroidectomy, obtained some temporary relief. One patient with fulminating Raynaud's disease with extreme pain and slight necrosis of finger tips was much improved either by iontophoresis or by cessation of smoking.

Untoward Effects. Undesirable effects of the drug were obtained in the case of 12 of the 42 patients. Atropine was needed only three times. The series of treatments of only 3 patients were discontinued (Cases 3, 10, 19). The single patient chosen for treatment with a history of asthma was at first able, and later unable, to tolerate 10 milliamperes for 10 minutes without having mild asthma precipitated (Case 3). Two patients with varicose ulcers each had two episodes of chills and fever, several hours after treatment, 1 to 103° (Cases 7, 10). The chills were probably caused by a transient bacteremia or toxemia resulting from greatly increased blood flow. One debilitated patient was barely able to tolerate 5 milliamperes for 10 minutes through a large decubitus ulcer (Case 19). Two patients who had no discomfort with 20 milliamperes for 20 minutes were later, at the 36th and 19th treatments, respectively, barely able to tolerate 5 milliamperes for 10 minutes because of severe local erythema (Cases 39, 41). One thrombophlebitic ulcer was painful when 10 milliamperes for 10 minutes was exceeded (Case 13). In another such patient temporary edema of the foot resulted, and in a third, superficial "flares" became excessively dilated in the skin area covered by the drug. Two patients complained, at several times during therapy, of a feeling of mild pressure under the sternum. No patient received a burn, against which precautions were taken, because when small electrodes were used they were used only with greatly reduced current, and because skin was constantly protected from metal of the electrodes.[7,8]

Discussion. Judging from the experience of this clinic, the pharmacologic effects of acetyl-β-methylcholine chloride iontophoresis are as described by Kovacs.[4a] There is consistently a great increase in blood flow, at least in the skin.[4a,8] Undesirable side effects of the drug are mild if there is no history of asthma or of recent infec-

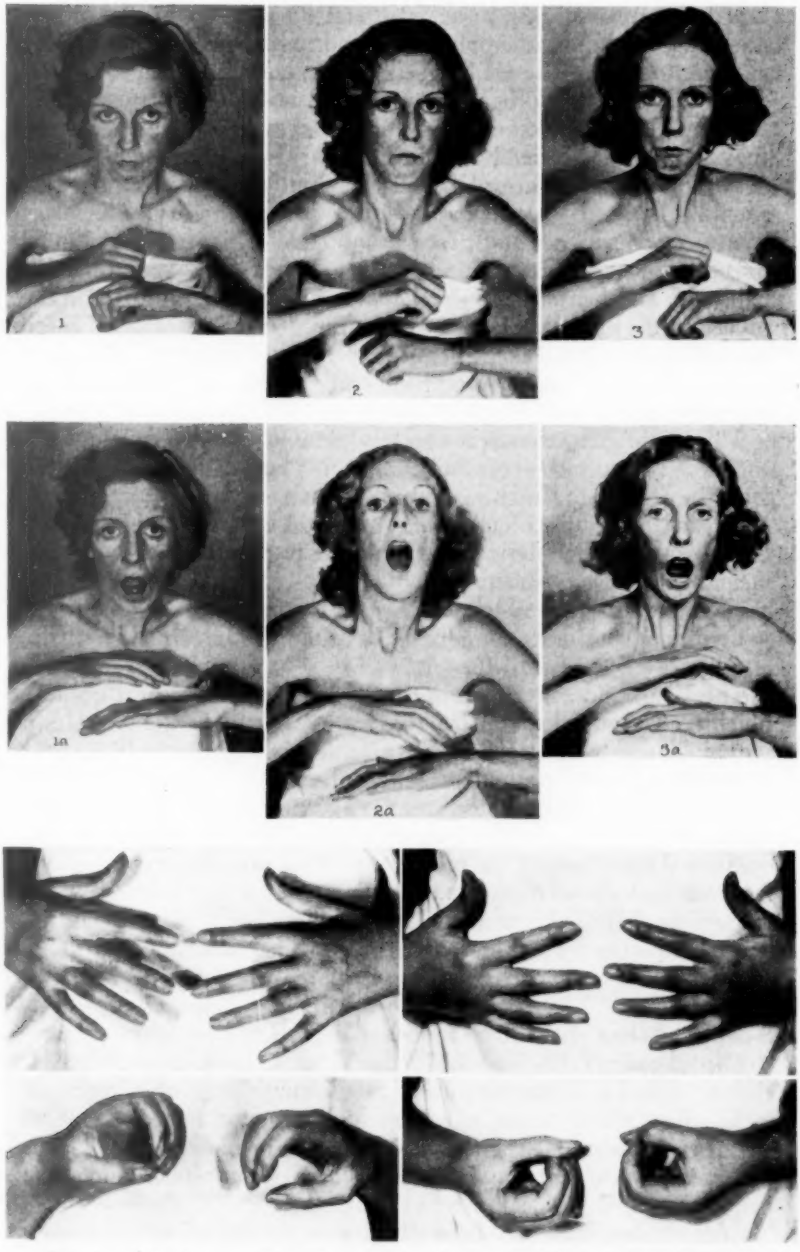

FIG. 4.—*Scleroderma.* Case 35, upper six photographs taken at three times, 1 and 1-*a* a week after starting iontophoresis, 2 and 2-*a* 10 months (improvement), and 3 and 3-*a*, 28 months after starting (slight relapse). Case 36, lower four photographs, left two taken at onset of iontophoresis, right pair taken 2 months later (slight improvement).

tion in the area of veins. The results of this therapy, however, were not as favorable as those previously reported. Longstanding, severe varicose ulcers were made less painful, cleaner, and smaller, but did not heal. The ulcers chosen were for the most part severe and this may explain the difference in results. Most of the other ulcers, post-thrombophlebitic, decubitus, and so forth, also failed to heal.

We believe that acetyl-β-methylcholine chloride iontophoresis should at times be used as an adjunct to the more usual forms of treatment of varicose and post-thrombophlebitic ulcers, but should be used only (1) after more direct methods such as supportive bandages and ligation of veins have failed, or (2) before the more severe forms of therapy such as prolonged bed rest or the Linton operation are undertaken. Its use preceding surgery lies mainly in the effect of cleaning ulcers: operative procedures can then be carried out with less danger of infection.

This clinic's experience in the treatment of scleroderma is much the same as that of Duryee and Wright.[3] There is usually some prolonged softening of the skin, some subjective improvement, but little effect on the mobility of limited joints. Very prolonged therapy is necessary. Scleroderma also tends to respond to other simpler means of causing peripheral vasodilatation such as heat and thyroid medication. A favorable response to iontophoresis of the single patient with localized scleroderma (morphœa) suggests further trial (see Table 1).

The best results were obtained in the case of chronic thrombophlebitis without ulcer. Murphy[9] has described a longer series. In most instances there was relief of afternoon discomfort. The effect is sufficiently prompt and of sufficient duration to recommend a trial of this therapy in these cases. The 2 instances in which dysmenorrhea was relieved by iontophoresis of the legs suggests a new occasional usefulness of the procedure. There are direct connections between the veins of the legs and the pelvic veins, and it is reasonable to suppose that blood carrying a relatively high concentration of the drug reaches the pelvic veins from the leg veins. Perhaps this causes dilatation of spastic pelvic vessels associated with other thrombosed pelvic vessels. There was no control in these cases using acetyl-β-methylcholine chloride by mouth. This should be done.

The cause of the beneficial clinical effect of acetyl-β-methylcholine chloride iontophoresis is unknown. The one pharmacologic effect which seems a reasonable cause for improvement of the diseases mentioned is the great increase in blood flow.[4a,8] It is only fair to state that equal or greater increases in rate of blood flow can be obtained by local or reflex heat.[8]

Brief studies with Dr. James Forrester, on the effects of acetyl-β-methylcholine chloride iontophoresis on the growth of bacteria in agar, show no appreciable antibacterial action when the concentration of the drug and of the current are similar to those used thera-

peutically. Saylor, Kovacs, Duryee, and Wright suggested that in addition to an increase in blood flow, diaphoresis may play a therapeutic rôle by relieving the tissues of an overload of fluid.[10] The present observations fail to substantiate any reduction in edema. Acetylcholine plays a normal physiologic rôle[2] and it may be that acetyl-β-methylcholine, introduced in high concentration locally by iontophoresis, has some unknown parasympathicomimetic action which favors healing.

Summary. Acetyl-β-methylcholine chloride iontophoresis greatly increases cutaneous blood flow and is a useful adjunct to the therapy of some non-arterial peripheral vascular disorders. The augmented blood flow may be the cause of the improvement. It is recognized that the disorders for which the procedure has been recommended are chronic and usually relapsing under most forms of accepted therapy. There is some beneficial result in some cases of scleroderma, but therapy must be continued over a long period of time. Varicose and post-thrombophlebitic ulcers tend to become smaller, cleaner, and less uncomfortable, but they usually fail to heal and the benefits are usually transient. The procedure is recommended for the treatment of these ulcers only after more direct measures have failed or before surgical treatment is instituted. It is not a substitute for surgical measures designed to correct incompetence of venous valves, but it does help improve ulcers sufficiently to make surgery safer. The best results are obtained in relieving post-thrombophlebitic discomfort. The dangers of acetyl-β-methylcholine chloride iontophoresis are remote, with the exception of burns which occur when electrode metal touches skin, or when the importance of the relation of the strength of the current to the size of the electrodes is not appreciated.

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BOOK REVIEWS AND NOTICES

CONGENITAL SYPHILIS. By CHARLES C. DENNIE, B.S., M.D., Professor of Dermatology, University of Kansas Medical School, Kansas City, Kansas; Chief of the Department of Dermatology and Syphilology of Bell Memorial Hospital, Kansas City, Kansas, etc., and SIDNEY F. PAKULA, B.S., M.D., Visiting Pediatrician to Children's Mercy Hospital, Kansas City General Hospital, Alfred Benjamin Clinic and Menorah Hospital, Kansas City, Mo. Pp. 596; 133 illustrations. Philadelphia: Lea & Febiger, 1940. Price, $8.00.

IN a comprehensive work with ample bibliography and excellent illustrations, the authors take cognizance of a need in present-day medical literature for an adequate text, dealing with all phases of the management of congenital syphilis from the treatment of the pregnant syphilitic woman to prevent infection of the unborn child, to the management of the adult congenital syphilitic. The historical introduction stressing the problems in the detection and eradication of a disease which is usually symptomless in the expectant mother, and seldom clinically manifest in the newborn child during the neonatal period, gives much food for thought. The chapter on congenital syphilis of the bones and joints, and the one covering the eye changes in the congenital syphilitic (the latter by John McLeod and A. N. Lemoine) are especially well done. The authors have had the same difficulties in obtaining reproductions of roentgenograms of early congenital syphilis with sufficient bone detail to be understandable to any but the experienced, that characterizes almost all American and some European publications.

Throughout the work the authors have drawn upon a vast clinical experience and large and varied patient material. The discussions of the various aspects of the field are amply illustrated with case experience, in a manner however which might occasionally, for some individuals at least, detract from the clarity of the presentation. It is, for example, rather difficult, in spite of the considerable discussion about serologic and roentgenographic interpretation, for the reader to obtain a clear and concise impression of the procedure to be followed in making the diagnosis of infantile congenital syphilis, a seemingly important aspect of the subject. Likewise, the chapter on treatment commences with the statement, "A definite diagnosis of congenital syphilis having been established," when it would seem that a brief summary discussion orienting the reader in the indications for treatment might be in order.

The authors show a tendency to take definite stands on some controversial points in the congenital syphilis field. Among possibly criticizable statements are:

1. The suggestion that all offspring of adequately treated mothers would be better off with a year of active postnatal treatment for syphilis and that "in every instance the infants who are the issue of inadequately treated mothers should be treated no matter what the serologic reactions." This statement is also apparently meant to convey the impression that every child in a family discovered to contain one congenital syphilitic should be treated regardless of the individual physical or serologic status.

2. The recommendation that women with symptomatic late syphilis, particularly tabes (p. 92), and young mothers with early resistant syphilis (p. 103) be aborted.

The general discussion of the serologic diagnosis of syphilis in infancy

seems considerably weakened by: 1, The failure of the authors to make direct mention of the quantitative titered Wassermann studies and conclusions of such authors as Faber and Black, Christie and J. A. V. Davies; 2, the apparent stress placed upon serologic diagnosis by multiplicity of positives (or negatives) in various antigens on the same specimen of blood rather than upon repeat specimens; and, 3, such statements as that a quantitative serologic reaction should be done on patients in whom the specific reagins are present in such small amounts that a qualitative reaction does not pick them up. This last is, of course, a matter of sensitivity of the test rather than of titration. The fact that the authors apparently consider the positive blood serologic test on the newborn child to be of absolute diagnostic import at the age of 3 weeks (p. 84), at the age of 2 weeks (p. 86), and at the age of 6 weeks (p. 88) is also a little confusing.

The authors' advice, on the other hand, against the use of mercury rubs in active infantile congenital syphilis and against the continuous energetic treatment over a period of years of the seroresistant asymptomatic late congenital syphilitic seem to conform to the best current viewpoints and are especially worthy of stress. N. I., Jr.

The Vasomotor System in Anoxia and Asphyxia. A Study of the Adjustment Reactions of the Mammalian Organism (Illinois Medical and Dental Monographs, Vol. II, No. 3). By Ernst Gellhorn, M.D., Ph.D., Professor of Physiology, and Edward H. Lambert, M.D. Pp. 71; 21 illustrations. Urbana, Ill.: The University of Illinois Press, 1939. Price, $1.00.

The authors of this monograph review the literature and include an excellent bibliography. They make a study, as measured by changes in blood pressure, of the effects of anoxia, excess carbon dioxide, and a combination of the two, on the vasomotor center of anesthetized artificially ventilated dogs. The major conclusion to be drawn from this work is that anoxia augments the response of the vasomotor center to carbon dioxide in the intact animal. Since this augmentation is also present after denervation of the carotid and aortic bodies it is due in part to direct stimulation of the vasomotor center by anoxia. The contribution would have been of more value if the authors had included blood gas studies and more data as to the constancy of these phenomena. P. D.

Developmental Anatomy. A Text-book and Laboratory Manual of Embryology. By Leslie Brainerd Arey, Ph.D., Sc.D., LL.D., Robert Laughlin Rea Professor of Anatomy, Northwestern University. Pp. 612; 590 illustrations, some in color. Fourth Edition, revised. Philadelphia: W. B. Saunders Company, 1940. Price, $6.75.

The author's *Developmental Anatomy* was written for medical students and since the appearance of the first edition it has been one of the favorite texts of students interested primarily in human embryology. The fourth edition not only carries on the tradition of the earlier ones, but its structure is even more substantial. Numerous figures have been added, some diagrammatic in nature, illustrating various phases or processes of development. Others give three-dimensional aspects of certain regions of the embryo. In addition, microphotographs have been included, giving valuable information to the student on early phases of development which cannot be studied in the laboratory. Although it contains numerous illustrations, the book is not overcrowded with pictures. A proper balance

has been preserved between text and figures. The text is as simple and clear as in the earlier editions; the changes are not corrections, but additions. The author has brought the material up to date, including all important discoveries in mammalian embryology reported since the publication of the third edition. Undoubtedly the book will be received by student and teacher with equal enthusiasm, for the reader realizes the serious effort involved in the preparation of such a volume. Only a sincere scientist, a good teacher and an expert publisher could produce such a fine book for medical students. G. de R.

A Review of the Psychoneuroses at Stockbridge. A Case Study and Statistical Analysis. By Gaylord P. Coon, M.S., M.D., Chief Medical Officer, Boston Psychopathic Hospital, and Alice F. Raymond, A.B., Statistician, Department of Child Hygiene, Harvard School of Public Health. Pp. 299; 2 figures and 66 tables. Stockbridge, Mass.: Austen Riggs Foundation, Inc., 1940.

This study is of the histories of patients treated during the years 1910–1934 and an evaluation of the therapeutic results. In the Berkshires, near the center of the old New England village of Stockbridge, are two houses with the outward appearance of quiet country inns. Within are quartered some 50 patients, unrestrained by barred windows or locked doors, and cared for by ununiformed nurses. Such "guests" as are able to be about partake of the town life as do the residents. Nearby are the doctors' offices, where others who are able visit their physician each day. There is an occupational therapy shop, indoor and outdoor games and sports, presided over by a recreational director. A group of 1060 patients—approximately 20% of those admitted—were studied and the diagnoses were almost invariably neurasthenia or anxiety neurosis. It is believed a marked imbalance of the instinctive drives and a high degree of hypersensitivity, are the main predisposing factors. The therapeutic approach is reëducation and is akin to the "persuasion" technique of Dubois together with the "psychobiological" concepts of Adolph Meyer. N. Y.

Progress in Medicine. A Critical Review of the Last Hundred Years. By Iago Galdston, M.D. With a Foreword by Henry E. Sigerist, M.D. Pp. 362. New York: Alfred A. Knopf, 1940. Price, $5.00.

Neither a conventional history of the medicine of the past century nor a digest of recent medical progress, this thoughtful work sketches with broad strokes the main medical trends of this prolific period. Ideas rather than heroes are stressed, though with the author's skillful handling sufficient personal touches are introduced to give some revealing pictures of the leading personalities as they appear. Microbes first hold the stage for 4 chapters, then a chapter on nutrition—but stressing the vitamins—another on the endocrines and the *milieu intérieur*, 2 on psychiatry, then "a century of clinical progress," illustrating some of the triumphs of diagnosis, preventive medicine and recent therapeutic successes. In a final chapter on "Whither Medicine" the author gives us some interesting views on what he calls personal preventive medicine, *i. e.*, "the development and realization of the individual's potentialities for growth, achievement and well being." Here he finds there is still plenty of room for improvement. We not only welcome this mature presentation as a source of entertainment, but also believe that it may help the reader to a better understanding of modern medical progress than he would perhaps get from a larger more detailed work. E. K.

THE CHRONICLE OF CRICHTON ROYAL (1833–1936). Being the Story of a Famous Mental Hospital During Its First Century, and Illustrating the Evolution of the Hospital Care and Treatment of Mental Invalids in Scotland. By CHARLES CROMHALL EASTERBROOK, M.A., M.D., F.R.C.P.E., Physician Superintendent, 1908–1937, and the late SIR JAMES CRICHTON-BROWNE, M.D., LL.D., F.R.S. Pp. 663; 103 illustrations and map. Dumfries, Scotland: Courier Press, 1940. Price, 25/.

BEGINNING about a century ago with the lavish endowment of 100,000 pounds, Crighton Royal has always maintained the highest possible standard of its care and treatment of those mentally afflicted. This chronicle gives the intimate details of that famous Scottish institution, which, as stated, will be of most interest to those who have been, are now, and shall be associated with the institution. N. Y.

THE HISTAMINE AND INSULIN TREATMENT OF SCHIZOPHRENIA AND OTHER MENTAL DISEASES. By HORACE HILL, M.R.C.P., Medical Superintendent, Laverstock House Mental Home, Salisbury, England. Pp. 133. Baltimore: The Williams & Wilkins Company, 1940. Price, $1.75.

IN this author's investigations, treatment was begun with insulin, then histamine alone was used, and finally their use was combined. Stating that histamine is found in all varieties of shock, he believes it is histamine and not shock that gives the favorable results. The method is described as having led to improvement in hitherto unimproved patients. Symptoms were lessened or entirely overcome in some severe and long-standing schizophrenic patients. Good results were also obtained in "other cases as manic-depressive melancholia, paranoiac conditions and especially in stupor." In old patients with thick and rigid arteries, the method is useless. When employed by competent physicians, the régime is not dangerous and not unpleasant. There are many brief case reports. The text is rather loosely written and there is the frequent misuse of the word "case" for "patient"—"case got well;" "case was not mine;" and, "case H's husband." N. Y.

THE FUNDAMENTALS OF NUTRITION. By ESTELLE E. HAWLEY, PH.D., and ESTHER E. MAURER-MAST, M.D., University of Rochester, School of Medicine and Dentistry, Rochester, New York. Including Table of 100-Calorie Portions, by ESTELLE E. HAWLEY, ESTHER E. MAURER and HERBERT F. VAN EPPS, The Department of Vital Economics, University of Rochester and discussions of the Dietary Management in Specific Conditions, by Collaborators associated or formerly associated with The University of Rochester, School of Medicine and Dentistry. With a Foreword by JOHN R. MURLIN, PH.D., SC.D., Professor of Physiology and Director of the Department of Vital Economics, University of Rochester. Pp. 477; illustrated. Springfield, Ill.: Charles C Thomas, 1940. Price, $5.00.

THIS book reports the experience gained in the Department of Vital Economics in the University of Rochester, particularly as regards the extensive instruction in nutrition now carried on in that school. The monograph presents both the fundamentals for the normal and a discussion of the diet management of specific conditions by 19 collaborators associated with the School of Medicine and Dentistry of the University. The text is ideal as a teaching manual.

The book is divided into five sections. The first deals with the fundamentals of metabolism and summarizes the energy requirements of the body. The second section considers the fundamentals of nutrition, classification

of foods, nature of the nutrient elements, normal diet and composition of low cost meals.

The third section covers diseases of metabolism, of the digestive tract and specific disease groups such as anemias, cardiovascular, food allergy and toxemia of pregnancy. There is an excellent section on the treatment of surgical patients, and one on vitamin deficiencies.

The fourth section, on the planning of diets, is based for simplicity upon the method of 100-calorie portions. The authors feel that the 100-calorie portion establishes a common basis for comparison and is easily visualized, since it is so frequently used as an "average serving" or is a simple multiple of it. In this section on diet planning there are numerous illustrations to explain the choosing of foods to make up the necessary equivalents of various elements.

In the appendix (Section 5) there is an excellent outline for the research worker in the evaluation of nutritional statistics. Special chapters on the study of milk, an analysis of commercial vitamin products, allergies and infections follow, and there are three chapters on diet instruction of patients, miscellaneous items and food suggestions for special conditions.

This volume not only is a good textbook for the medical student or nutritionists, but should also be regarded as a reference volume by research workers, dietitians and practising physicians. P. W.

INTRODUCTION TO MEDICINE. By DON C. SUTTON, M.S., M.D., Associate Professor of Medicine, Northwestern University School of Medicine; Attending Physician, Medical Division of the Cook County Hospital, etc. With Introduction by ADA BELLE MCCLEERY, R.N., Superintendent, Evanston Hospital, Evanston, Ill. Pp. 642; 144 illustrations and 14 color plates. St. Louis: The C. V. Mosby Company, 1940. Price, $3.25.

As a textbook for the beginning student nurse this book would not be suitable. The author attempts to cover too many subjects and consequently is entirely too brief to be accurate. For instance in the chapter on the "Functional Nervous Disorders" he covers "Hysterical Fits" in three lines. It is a mistake for any one to believe that one textbook could adequately cover the variety of subjects included in this book. As a reference book the illustrations would be very useful. M. S.

A TREATISE ON MEDICO–LEGAL OPHTHALMOLOGY. By ALBERT C. SNELL, M.D., Lecturer in Ophthalmology, School of Medicine and Dentistry, University of Rochester; Consultant in Ophthalmology, Strong Memorial and Rochester General Hospitals, etc. Pp. 312; illustrated. St. Louis: The C. V. Mosby Company, 1940.

COMPENSATION of industrial accidents makes it necessary for the examining physician to give expert opinion concerning eye injuries to non-medical groups. This is also true of eye injuries arising as a result of the increasing number of motor accidents.

It is important therefore for all ophthalmologists to know the essential rules of evidence, forms of legal procedure, and his own rights and obligations as a medical witness. This book sets forth these problems in medical jurisprudence and should be extremely valuable for all who practice ophthalmology.

In addition, the author has set forth the result of his years of study and research on the evaluation of functional loss of the eye. He presents a method by means of which the loss of useful visual function can be presented accurately on a percentage basis. F. A.

ROSE AND CARLESS MANUAL OF SURGERY. American (Sixteenth) Edition, edited by WILLIAM T. COUGHLIN, B.S., M.D., F.A.C.S., Professor of Surgery and Director of the Department of Surgery, St. Louis University School of Medicine; Surgeon-in-Chief, St. Mary's Group of Hospitals, St. Louis. From the Sixteenth English Edition by CECIL P. G. WAKELEY, D.Sc., F.R.C.S., F.R.S.E., F.R.S.A., F.A.C.S., F.R.A.C.S., Fellow of King's College, London; Senior Surgeon, King's College Hospital; Temporary Surgeon-Rear-Admiral, etc., and JOHN B. HUNTER, M.C., M.CHIR. (CANTAB.), F.R.C.S. (ENG.), Surgeon, King's College Hospital, etc. Pp. 1656; 1034 illustrations and 30 plates (some in color). Baltimore: The Williams & Wilkins Company, 1940. Price, $9.00.

THE fact that this is the sixteenth American edition is evidence of the continuing popularity of this "manual." Manual is hardly an appropriate term since it has become expanded to the full dimensions of a textbook over the years.

While it has been kept fairly up to date in methods or treatment, it lacks the physiologic approach to the problems of surgery that several of the modern American textbooks now have. This is a volume which will, at least in this country, be used more frequently by surgeons than by medical students, for it is now too large to be used for third and fourth year students.

I. R.

FEEDING THE FAMILY. By MARY SWARTZ ROSE, PH.D., Professor of Nutrition, Teachers' College, Columbia University. Pp. 421; illustrated. Fourth Edition. New York: The Macmillan Company, 1940. Price, $3.75.

IN this well-known volume, the author has recognized the advances in the solution of dietary problems in recent years, particularly in regard to allergy, which now forms the new chapter. Of particular importance to the head of the family, for whom this book is intended, are chapters on the cost of food, making the menus, and food for the family group. The author discusses the requirements of the various food factors for the different ages in a separate chapter. There are 6 chapters devoted to various diets for children from infancy to adolescence, and the requirements for adults and senile individuals are also portrayed. In the various diets which have been presented in different classes, he has specified not only the fuel values and cost but weight and protein caloric value as well, and in such a manner that they should be easily understood by persons of average intelligence. There is a well-developed chapter on food for the sick and convalescent. An appendix on nutritive values of foods and diet recipes contain much practical information. This book is highly recommended to the laity.

P. W.

SURGERY OF THE HAND. By R. M. HANDFIELD-JONES, M.C., M.S., F.R.C.S., Surgeon to Outpatients, St. Mary's Hospital; Senior Surgeon, Florence Nightingale Hospital, etc. Pp. 140; 95 illustrations (several in color). Baltimore: The Williams & Wilkins Company, 1940. Price, $4.50.

THIS short monograph makes no attempt to take the place of the classic monograph on the surgery of the hand by the late Allen B. Kanavel. It is in fact dedicated to him. It stresses the improvements in treatment in this field in a splendid manner. The paper and format are excellent. The illustrations are as fine as any the Reviewer has seen. Although the discussion is brief it is adequate. Here is a monograph that every intern, general practitioner and surgeon can own with pride.

I. R.

A Surgeon's Life. The Autobiography of J. M. T. Finney. Pp. 396; 1 illustration. New York: G. P. Putnam's Sons, 1940. Price, $3.50.

In this increasingly industrial and mechanical age we often ponder the question as to whether one of the many things that have been sacrificed may be the development of the rich and colorful personalities that were not uncommon in the past but seem so rare as we look about us. Perhaps it is the experience of each generation to feel so about contemporaries, but as one reads the author's account of "A Surgeon's Life" and is aware of the mellow, full character that emerges from its pages, one wonders whether the present and future will permit this personal development.

The author has lived in a period of great strides in the development of surgery and he was associated with one of the great leaders in this development, William Stewart Halsted. This autobiography makes the "great four" of Johns Hopkins Medical School, Osler, Halsted, Welch and Kelly, live again. The vividly told anecdotes of these men and their associates are a real contribution.

The author has well pointed out that emphasis on the science of surgery to the exclusion of the art of surgery may be fraught with grave danger. No one could realize this better than the author, whose knowledge of the human side of medicine is unsurpassed by any living surgeon.

The author reveals his character on every page of this book—his kindly humor, his appreciation of the humor of others, his tempered judgment, all of the characteristics that are known and appreciated by every younger surgeon who had had the privilege of contact with him. I. R.

The Neuroses in War. By several authors under the editorship of Emanuel Miller, M.D. (Cantab.), M.R.C.P., D.P.M. (Camb.), with a concluding chapter by H. Crichton-Miller, M.D., F.R.C.P. Pp. 250. New York: The Macmillan Company, 1940. Price, $2.50.

This book is the collaborated work of 11 neuropsychiatrists and an anonymous contributor, who "believe there is a very high degree of agreement over subjects which still remain somewhat controversal." If this be true, it is an achievement. The subject matter is discussed in 11 chapters and an appendix, as follows: A Survey of the Literature of Neuroses in War; Mode of Onset of Neuroses in War; Clinical Case Studies and Their Relationships; Differential Diagnosis of the Psychoneuroses of War; Psychopathological Theories of Neuroses in Wartime; Treatment of Neuroses in the Field; The Advanced Psychiatric Center; Treatment by Suggestion and Hypo-analysis; Technique of Other Psychotherapeutic Methods; Psychiatric Organization in the Services; The "War of Nerves;" Civilian Reaction, Morale and Prophylaxis; General Conclusion; Appendix A: Extracts From the "Report of the War Office Committee of Enquiry on Shell Shock" (1922). B: Description of the Treatment Facilities for Civilian Psychoneurotic Casualties Provided by the Emergency Medical Service (1940). C: Classification of Psychological Disorders in War. D: Psychiatric Pharmacology.

War neuroses may be treated by suggestion, reëducation, persuasion and by hypoanalysis. In hypoanalysis the effort is to release repressed fears through hypnosis, and to have the patient re-live his traumatic experiences; then, through suggestion, the necessary adjustment follows. Psychiatric pharmacology is an important section. It includes the method for narcoanalysis through the use of evipan-sodium; by thus overcoming resistance, emotions repressed at the time of the trauma because of some restraining influence, may then through suggestion be brought into the field of full consciousness. The method is not without danger and should only be employed by experienced physicians. Psychoanalysis in the Freudian sense is not recommended. The survey of literature is excellent, the bibliography is pertinent but the index is brief. N. Y.

NEW BOOKS.

Bacillary and Rickettsial Infections. Acute and Chronic. A Textbook. Black Death to White Plague. By WILLIAM H. HOLMES, Professor of Medicine, Northwestern University Medical School, etc. Pp. 676. New York: The Macmillan Company, 1940. Price, $6.00.

Foreign Bodies Left in the Abdomen. The Surgical Problems, Cases, Treatment, Prevention. The Legal Problems, Cases, Decisions, Responsibilities. By HARRY STURGEON CROSSEN, M.D., School of Medicine, Washington University, and DAVID FREDERIC CROSSEN, LL.B., School of Law, Washington University, St. Louis. Pp. 762; 212 illustrations, including 4 color plates. St. Louis: The C. V. Mosby Company, 1940. Price, $10.00.

The Doctor and the Difficult Child. By WILLIAM MOODIE, M.D., F.R.C.P., D.P.M., Medical Director, London Child Guidance, Clinic and Training Centre. Pp. 214. New York: The Commonwealth Fund, 1940. Price, $1.50.

Psychotherapy. Treatment That Attempts to Improve the Condition of a Human Being by Means of Influences That Are Brought to Bear Upon His Mind. By LEWELLYS F. BARKER, M.D., Emeritus Professor of Medicine, Johns Hopkins University; Visiting Physician, Johns Hopkins Hospital, Baltimore. Pp. 218. New York: D. Appleton-Century Company, Inc., 1940. Price, $2.00.

The Diagnosis and Treatment of Diseases of the Heart. By HENRY A. CHRISTIAN, M.D., Sc.D. (HON.), LL.D., F.A.C.P., HON. F.R.C.P. (CAN.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University; Physician-in-Chief, Emeritus, Peter Bent Brigham Hospital, Boston. (Reprinted from Oxford Monographs on Diagnosis and Treatment.) Pp. 599; 28 figures. New York: Oxford University Press, 1940.

The Endocrine Function of Iodine. By WILLIAM THOMAS SALTER, Assistant Professor of Medicine, Harvard Medical School; Associate Physician, Thorndike Memorial Laboratory, Boston City Hospital. Pp. 351; 40 figures and 45 tables. Cambridge, Mass.: Harvard University Press, 1940. Price, $3.50.

From Thirty Years With Freud. By THEODOR REIK. Translated by RICHARD WINSTON. Pp. 241. New York: Farrar & Rinehart, Inc., 1940. Price, $2.50.

Diagnosis and Treatment of Menstrual Disorders and Sterility. By CHARLES MAZER, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania; Gynecologist to the Mount Sinai Hospital, Philadelphia, and S. LEON ISRAEL, M.D., F.A.C.S., Instructor in Gynecology and Obstetrics, School of Medicine, University of Pennsylvania; Associate Gynecologist to the Mount Sinai Hospital, Philadelphia. Pp. 485; 88 illustrations and 1 colored plate. New York: Paul B. Hoeber, Inc., 1941. Price, $6.50.

Medical Index of Hospital Equipment, Medical Supplies, Surgical Instruments and Orthopedic Appliances, Volume 1, No. 1, December, 1940. Pp. 13; illustrated. New York: Medical Index, Inc., 1940. Price, 25c single copy; $2.00 per year.

Offered as "the only publication in the profession field, devoted exclusively to the tools of medical practice and surgery."

Diagnosis and Treatment of Arthritis and Allied Disorders. By H. M. MARGOLIS, M.D., M.S. (in med.), F.A.C.P., Chief, Arthritis Service, St. Margaret Memorial Hospital; Associate in Medicine, Montefiore Hospital; Consultant in Medicine, Pittsburgh Diagnostic Clinic. Pp. 551; 140 illustrations. New York: Paul B. Hoeber, Inc., 1941. Price, $7.50.

Clinical Pellagra. By SEALE HARRIS, M.D., Professor Emeritus of Medicine, University of Alabama, Birmingham, assisted by SEALE HARRIS, JR., M.D., Formerly Assistant Professor of Medicine, Vanderbilt University, Birmingham, Ala. With a Foreword by E. V. MCCOLLUM, PH.D., SC.D., LL.D., Professor of Biochemistry, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore. Pp. 494; 66 illustrations and 16 tables. St. Louis: The C. V. Mosby Company, 1941. Price, $7.00.

Physiology of the Fetus. Origin and Extent of Function in Prenatal Life. By WILLIAM FREDERICK WINDLE, Professor of Microscopic Anatomy, Northwestern University Medical School. Pp. 249; 70 illustrations and 27 tables. Philadelphia: W. B. Saunders Company, 1940. Price, $4.50.

Doctrina y Practica de la Profilaxis de la Tuberculosis. By LUIS SAYÉ, Profesor de la Universidad de Barcelona; Director del Servicio de Examen de Colectividades del Ministerio de Salud Pública del Uruguay. Pp. 355; 170 illustrations. Buenos Aires: Editorial Sudamericana, S. A., n.d.

The four sections of this work are devoted to: 1, epidemiologic investigations; 2, the technique and results of B.C.G. vaccination; 3, Abreu's method of radiophotography in the diagnosis of tuberculosis; 4, prophylaxis of tuberculosis.

Bacteriology in Neuropsychiatry. A Survey of Investigations Concerned With the Specified Role of Infectious and Immune Processes. By NICHOLAS KOPELOFF, PH.D., Research Bacteriologist, New York State Psychiatric Institute and Hospital, New York. Pp. 316. Springfield, Ill.: Charles C Thomas, 1941. Price, $4.50.

A Textbook of Clinical Neurology. By J. M. NIELSEN, B.S., M.D., F.A.C.P., Associate Clinical Professor of Medicine (Neurology), University of Southern California; Senior Attending Physician (Neurology), Los Angeles County General Hospital; Attending Neurologist, Hospital of the Good Samaritan, Los Angeles. Pp. 672; 179 illustrations. New York: Paul B. Hoeber, Inc., 1941. Price, $6.50.

The Medical Reports of John Y. Bassett, M.D. The Alabama Student. With an Introduction by DANIEL C. ELKIN, M.D., Joseph B. Whitehead Professor of Surgery, Emory University. Pp. 62; illustrated. Springfield, Ill.: Charles C Thomas, 1941. Price, $1.50.

NEW EDITIONS.

Methods of Treatment. By LOGAN CLENDENING, M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, University of Kansas Hospitals, and EDWARD H. HASHINGER, A.B., M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, University of Kansas Hospitals, and St. Luke's Hospital, Kansas City, Mo. With Chapters on Special Subjects by 12 Contributors. Pp. 997; 138 illustrations. Seventh Edition. St. Louis: The C. V. Mosby Company, 1941. Price, $10.00.

The Merck Manual of Therapeutics and Materia Medica. A Source of Ready Reference for the Physician. Pp. 1436. Seventh Edition. Rahway, N. J.: Merck & Co., Inc., 1940. Price, $2.00.

This convenient compend is now brought down to date by the inclusion of 12 new chapters and of new remedies such as the sulfonamide derivatives, suprarenal cortex, nicotinic acid, and numerous others that have become available since the last edition was published (1934). It seems quite adequate and authoritative and should be very useful for the purpose for which it was intended, *viz.* to make available in compact form the bare essentials of diagnosis and treatment of important diseases. C. S.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY.

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HEPARIN.

In 1916, McLean,[10] while working on cephalin in Howell's laboratory, reported isolating an active anticoagulant from liver tissue. Howell[6a] studied this substance, giving it the name "heparin," and concluded that it was probably a glycuronic acid derivative. For some time heparin was used in laboratory experiments as an anticoagulant but it was found to be toxic when given in any quantity to animals. Mason,[11] Howell,[6b] and Godlowski[4] have reported the use of heparin in transfusions. Mason found toxic reactions in about half of his patients, though with the more highly purified heparin less of the substance was needed and reactions were fewer. Howell used a fairly potent preparation. Godlowski, using small amounts of heparin, found no evidence of toxicity.

In 1933, Charles and Scott[3] and Schmitz and Fischer[14] published their studies on the analysis and preparation of purified heparin. The method devised by Charles and Scott made it possible for the Connaught Laboratories to produce a purified crystalline barium salt with a potency of about 500 Howell units per milligram, or 100 units according to their own standardization. For some time heparin for clinical use has been made in Canada, Sweden and Switzerland. The price, however, was so high that the general clinical use of heparin was impractical. It has since been made by the Connaught Laboratories at a price which permits its wider use when indicated. Within the past few months it has been made by an American firm and soon will be made by several other companies.

A review of the history and chemistry of heparin with a full bibliography to that date can be found in the article of Morton F. Mason.[12] It would be repetitious to reprint it here, so we shall confine ourselves to the present clinical uses of heparin.

Administration. Purified heparin can be administered locally, subcutaneously or intravenously. It is unfortunate that there is no agreement on the standardization of this substance so that amounts in units

cannot be given without specifying the particular preparation. Best[1] says "A unit has never been defined exactly. It is usually stated to be the amount of anticoagulant which inhibits for 24 hours the clotting of 1 cc. of blood under certain conditions of temperature and so forth. We have suggested as a provisional unit the activity contained in 0.01 mg. (10 γ) of the barium-free material, that is, 100 units per mg. This would make a convenient unit from both the physiological and the clinical aspect." This unit is accepted for the preparation of the Connaught Laboratories, but the units of the Swedish and Swiss preparations are not the same. The Best unit is equal to about 5 of the Howell cat units.

The dosage will vary according to the response of the patient but as a rule 20 to 30 units (Best) per kg. per hour will keep the clotting time at about a 20- to 30-minute level. The dose should be controlled by repeated estimations of the clotting time of the patient's blood. We have found the Lee-White method very satisfactory for determining the coagulation time.

In connection with the dosage and administration of heparin, it is well to keep in mind the fact that protamine has an antagonistic effect and will quickly neutralize the anticoagulant effect of heparin. If, after heparinization, a hemorrhage should start, or an immediate operation should become necessary, the normal clotting time of the blood can be rapidly restored by the administration of protamine. Jaques, Charles and Best[7] say "There appears to be a direct proportionality between protamine and heparin, 1 mg. of protamine neutralizing 0.3 mg. of heparin. The heparin effect is annulled if the heparin is injected within approximately 1 hour after the protamine. On the other hand, if the anticoagulant is administered more than an hour after protamine the neutralizing effect of the latter is not observed."

The local use of heparin, incorporated in vaseline, in the suture of vessels has not had any success. Regional heparinization has been of value in experimental work and may well be of some clinical value. Small amounts of heparin are injected proximal to the site of vessel suture, so that the clotting time of the blood is increased before it reaches the operative field. If the amount used is small the clotting time of the blood in other limbs or areas will not be affected.

Heparin may be administered subcutaneously but larger doses are required and the level of clotting time cannot be controlled satisfactorily. The most effective and best controlled method of administration is by continuous intravenous infusion, the amount being governed by repeated determinations of the clotting time of the blood.

When a single dose of heparin is given intravenously there is a rapid but transitory effect on the clotting time. In order to obtain an effect for as much as an hour a relatively large dose of heparin is required, the clotting time is high immediately after the injection, returning to normal somewhat abruptly after an hour or so.

When heparin is given continuously the desired level of clotting time can be maintained for as long as necessary, that is, over a period of days or even weeks. An initial injection to establish a high level may be desirable, the level being maintained by the continuous intravenous infusion.

Indications for the Clinical Use of Heparin. While heparin has been used in the experimental laboratory for some years for a variety of studies, its clinical value is just beginning to be appreciated, and it is quite possible many more indications for its use will develop.

Our own experience with heparin has been in the removal of emboli by arteriotomy and in the treatment of thrombosis and embolus in general. One of us (I. S. R.) had the opportunity of demonstrating the value of heparin following the removal of a saddle embolus from the bifurcation of the aorta, which occurred 14 days after a coronary occlusion in a man of 32. Heparin was given continuously for 13 days. It is now 2 years since the operation and the patient is actively at work, with normal lower extremities. Since "the chief handicap to this form of treatment and one which provides the strongest argument for those in favor of the conservative treatment, is that not infrequently the site at which the embolus is lodged, as well as the point at which the vessel is opened, becomes thrombosed again," it is evident that heparin is "an agent which would entirely change the prospects of" an operation of this type "by keeping the lumen of the vessel patent after the embolus was removed."[13b] Murray,[13c] in 1936, reported 12 successful arterial embolectomies in which heparin was used.

Following the lodgment of an embolus there occurs marked vascular contraction distal to the embolus and within a short time a thrombus begins to form on the embolus. The thrombus extends most rapidly in the proximal direction. Thus, two factors operate further to reduce the rate of blood flow to the affected part. If vascular contraction can be relieved in part by intravenously injected papaverine or by paravertebral sympathetic injection, and the heparin prevent the extension of the thrombus many extremities can be saved even without surgery. The same principles undoubtedly apply to other anatomic areas such as the abdomen and chest. It is upon this basis that much of our therapy has been conducted.

Encouraging results have followed the use of heparin in the conservative treatment of mesenteric thrombosis, pulmonary embolism and thrombosis in the extremities. One of us (I. S. R.) has treated 2 cases of mesenteric thrombosis, both of whom recovered without resection even though there were clinical signs of massive involvement of the gut. Murray[13a] has reported that "in the opinion of many surgeons, and from the literature on the subject the mortality rate in this disease is between 85 and 95 per cent. Most surgeons have never seen a case requiring resection of the bowel recover. In the face of these odds, it probably is a significant fact that the first 4 cases recovered without complications and are still alive and well. The next 2 cases had no further gangrene of bowel and died of other complications. Of all the clinical tests to which heparin has been put, this one is probably the most severe, and one is glad to report that the results have been most satisfactory." Thrombosis of the central vein of the retina has been treated successfully with heparin,[2,5] the heparin possibly preventing extension of the process, and furthering resorption of the hemorrhage.

It is difficult to evaluate the results of heparinization in pulmonary embolus for recovery follows a varying percentage of these accidents. We have seen several patients with clinical evidence of a massive embolus recover, however, following heparinization.

Whipple[15] and Murray[13b] have reported that the postoperative use of heparin will prevent the portal thrombosis which occasionally is observed following splenectomy for Banti's syndrome or familial jaundice.

The use of heparin in coronary thrombosis has been very limited. It is likely that heparin, if used early, would prevent the extension of the thrombosis in the coronary vessels and in addition prevent a thrombus upon the endocardium adjacent to the infarcted area. If this can be accomplished it will reduce greatly the incidence of secondary emboli and the extent of the infarction, and as a consequence reduce the mortality of the lesion.

A promising extension of the use of heparin is suggested by Lehman and Boys[8a,b] in their reports on "The Prevention of Peritoneal Adhesions With Heparin." Using rabbits they studied the formation of adhesions following mechanical trauma and bacterial contamination. After both mechanical trauma and bacterial contamination all the rabbits in each group developed adhesions. When heparin in salt solution was introduced into the peritoneal cavity, one rabbit (1%) of the traumatized group and none of the contaminated group developed adhesions. In the dog, adhesions were induced by bacterial contamination and then divided. "In all the control dogs a greater number of adhesions reformed than were divided" (157% average). "The heparin-treated animals presented only 25 per cent of the number of the original adhesions. The numerical difference is less striking than the observed difference at celiotomy. In the control animals, the reformed adhesions were largely extensive bands or sheets of adherence. In the heparin animals, the reformed adhesions were uniformly minute points of attachment, largely of omentum to the knots of silk ligatures." The further studies of this aspect of heparin treatment will be followed with interest

The treatment of infected thrombi with heparin and chemotherapy is just now developing. The report of Lyons[9] of 2 patients with bacteriemic staphylococcal cavernous sinus thrombophlebitis is encouraging for this condition is, as a rule, fatal. Whether further treatment of endocarditis with heparin and chemotherapy will bear out some of the earlier favorable reports is still a question.

The whole field of heparin therapy offers a challenge, for undoubtedly as we become more familiar with this substance, new uses for it will become evident.

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OPHTHALMOLOGY.

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RIBOFLAVIN AND KERATITIS.

ALTHOUGH several experimental workers had called attention previously to the occurrence of inflammatory conditions of the eyes and eyelids in young albino rats kept on a diet deficient in riboflavin, the specific association of conjunctival and corneal lesions with riboflavin deficiency in man apparently had not been noted prior to the year 1939. It is true that, as noted by Sebrell,[10] early Italian writers on pellagra, notably Soler in 1791 and Rampoldi in 1885, refer to such eye symptoms as inflammation of the cornea and corneal ulcers and opacities. In this country Clark reported pain in the eyes, conjunctivitis, failing vision and iritis in pellagrins, and Whaley mentioned photophobia, mydriasis, and superficial inflammation of the cornea. In the light of present knowledge, these lesions might be interpreted as manifestations of riboflavin deficiency. But the first definite statement relating clinical ocular disease to riboflavin deficiency would appear to be that of Spies, Bean and Ashe in May, 1939. They stated that some patients with riboflavin deficiency complain of a disturbance of vision which disappears in 4 to 6 days following the administration of adequate amounts of riboflavin. This rather indefinite statement is made somewhat more definite in a paper published by Spies, Vilter and Ashe[12] in September, 1939. They called attention to an "undescribed manifestation of a deficiency state," "a lesion of the eyes characterized by bulbar conjunctivitis, lacrimation, burning of the eyes, and failing vision," which yielded to riboflavin therapy. Since that time a number of articles have appeared which describe this syndrome more accurately.

Lesions of the Cornea in Experimental Animals. According to Day, Langston and O'Brien,[3] Goldberger and Lillie reported in 1926 that rats on diet deficient in vitamin G developed loss of hair around the eyelids and excess secretion from the conjunctiva; Chick and Roscoe stated in 1927 that young rats showed alopecia around the eyelids followed by conjunctivitis and ophthalmia after several weeks on vitamin G deficient diet; Salman, Hays and Guerrant in 1928 reported lacrimation, ptosis, alopecia of eyelids, conjunctivitis and opaque eyeballs in rats on a similar diet. However, these last authors stated that the cornea was rarely involved and that the opacity observed was usually in the vitreous and sometimes in the lens. Likewise, in 1928, Findlay stated that the corneas remained normal but that alopecia and swelling of the lids and conjunctivitis developed in vitamin G deficient rats. In 1929 Sherman and Sandel[11] reported "sore eyes" with alopecia and abnormal secretion from the conjunctiva in their vitamin G deficient rats; and in a later

article in 1931 they included a report by Pappenheimer on the histologic examination of the cornea of one of these rats, "a very slight keratitis with corneal corpuscles, a few neutrophils, and some new-formed blood channels." Also in 1931 Thatcher, Sure and Walker reported that ophthalmia occurred in 15% of rats on a vitamin G deficient diet. Langston, Day and O'Brien reported, also in 1931, on the ocular changes in 37 rats. They found alopecia of the eyelids in 68%, lacrimation in 60%, conjunctivitis in 96%, anterior interstitial keratitis in 100%, and cataract in 94%. During the stage of acute inflammation microscopic examination of the lids showed moderate infiltration of the skin and subcutaneous tissues with lymphocytes and neutrophils and hemorrhagic areas. The corneas appeared clear in some cases, slightly clouded in others, and showed superficial vascularization in most cases. Microscopic examination revealed an inflammatory process in the anterior stroma. The epithelium was normal but small lymphocytic and leukocytic infiltrates accompanied by new vessel formation were found directly under the epithelium. In the later stages the lids were found to be normal except for alopecia, but the corneas showed small areas of scar tissue with new-formed blood-vessels in the anterior stroma visible both on loupe and microscopic examination.

In 1935 Bourne and Pyke[2] attempted to repeat the observations of Langston, Day and O'Brien on the development of cataract in rats fed a diet deficient in vitamin G. They were able to produce cataracts in only 31% of the animals after a period of 79 days on the diet. They stated that the most consistent ocular symptoms was "superficial keratitis" which occurred within 70 days in 92 to 100% of the rats. In nearly all cases this inflammatory condition cleared up as the experiment progressed, leaving the cornea clear, although vascularization and residual scarring of the cornea were observed in a few cases. In some animals the inflammatory condition recurred.

In 1939 Eckardt and Johnson,[5] also in the course of a study on nutritional cataract, noted keratitis or vascularization of the cornea in 12 of 23 rats on a riboflavin deficient diet. They were inclined to attribute little importance to these changes since they believed them to be transitory and not characteristic of riboflavin deficiency. However, the specific relationship of these corneal changes to riboflavin deficiency became apparent when, in a second series of animals, it was noted that all rats which survived to the 48th day showed either keratitis or vascularization of the cornea.

A detailed study of the corneal vascularization occurring in rats on diet deficient in riboflavin has been made by Bessey and Wolbach.[1] They state, "Vascularization of the cornea is an early and constant phenomenon in albino rats in riboflavin deficiency. It precedes all other demonstrable lesions of the deficiency." It was found in over 300 rats during a period of more than 2 years. Microscopic examination or India ink injections never failed to show it after the 4th week of riboflavin deficiency. With regard to the progress of the ocular lesions they stated that in 5 to 7 weeks the palpebral fissures become noticeably smaller, the eyeballs appear less prominent and even sunken in the orbits, the

lids become swollen, and a serous, blood-tinged conjunctival discharge develops. The corneas become slightly dull as if finely sanded and by the end of the 10th week the corneas may be turbid or white.

By the end of the 4th week slit-lamp examination shows a marked radial ingrowth of capillaries into the cornea from the vessels of the limbus. By the end of the 10th or 11th week these blood-vessels extend inward more than one-third the diameter of the cornea and some may reach the center. Apparently simultaneous growth takes place from both arterial and venous sources. At first the capillaries lie just beneath the corneal epithelium, but soon others invade the deeper layers of the stroma. Cloudiness of the cornea develops only several days or weeks after vascularization has occurred. Moderate degrees of cloudiness disappear as soon as 12 hours after large doses of riboflavin by mouth. After 2 weeks' treatment with riboflavin blood-vessels can no longer be seen with the slit-lamp but they can still be demonstrated by microscopic examination or India ink injection. They have been observed after 58 days of adequate riboflavin therapy but in diminished numbers, size and length.

The corneal epithelium remains unchanged until late in the deficiency state. It then shows degenerative changes, probably secondary to the lesions in the stroma. Leukocytes, chiefly polymorphonuclears, may be found in small numbers in the corneal stroma within a week or two after the vessels have penetrated the cornea. They gradually increase in numbers and may accumulate beneath the epithelium and later invade the epithelium. Vesicles may form between the superficial and deep layers of the epithelium and necrosis and ulceration of the cornea may be terminal results.

Similar vascularization of the cornea has been observed by Wolbach and Howe in vitamin A deficient rats. However, in these animals the vascularization seemed to occur in association with or following hyperkeratinization of the corneal epithelium and not as a primary growth of vessels as in riboflavin deficiency.

Bessey and Wolbach suggest that the vascularization of the cornea observed in experimental riboflavin deficiency is a response to asphyxiation of the corneal stroma. This view is supported also by Johnson and Eckardt.[7a,b,c] They state that riboflavin is believed to be an essential constituent of the oxidation system of Warburg's yellow enzyme. Since the cells are incapable of synthesizing riboflavin it must be continually supplied from exogenous sources to replace that lost in the urine and other excretions. It is believed that if hemin substances are not present in a tissue, such as the avascular cornea, oxidation within the cells is accomplished by Warburg's yellow enzyme. Hence, when riboflavin is deficient or absent the oxidation system of the cornea is seriously impaired. Johnson and Eckardt think that proliferation of capillaries from the limbus into the cornea is readily explained as an attempt by the cornea to overcome local asphyxia by bringing available oxygen in the blood into closer proximity with the corneal cells. Regression of the vessels from the cornea when riboflavin is supplied follows the restoration of the Warburg's yellow enzyme system to its normal position in the process of oxidation. Since riboflavin is destroyed when the hydrogen ion concentration of the tissue fluids is on the basic side,

Johnson and Eckardt think that gastric achlorhydria is a factor in clinical riboflavin deficiency. They state also that since riboflavin is inactivated biologically by light, exposure to sunlight hastens vascularization of the cornea.

Keratitis in Clinical Riboflavin Deficiency. In line with the early reports previously mentioned, Sydenstricker, Geeslin, Templeton and Weaver[13] in November, 1939, in describing their cases of riboflavin deficiency in human subjects, stated that in one of their patients the palpebral and scleral conjunctiva was very red with a small amount of serous exudate from the conjunctival sac and there was extreme photophobia. They did not mention keratitis. About the same time Pock-Steen[9] reported on the eye symptoms in 109 patients with leiodystonia, sprue, and sprue-like disorders. They all complained of reduced visual acuity during weak light such as twilight and inadequate artificial illumination. This "twilight blindness" differed from nightblindness in that it was not influenced by administration of vitamin A but was greatly improved a few hours after the administration of approximately 1 mg. of riboflavin. Sixty-seven of the patients improved after one injection of riboflavin, 31 improved after a longer period of treatment, and 11 did not improve. Among other symptoms in these patients Pock-Steen mentioned mydriasis, conjunctival irritation, keratitis, and disturbances of accommodation. He attributed the eye symptoms partly to ariboflavinosis and partly to histamine toxicosis.

In January, 1940, Kruse, Sydenstricker, Sebrell and Cleckley[14] reported on the ocular symptoms in 9 patients with clinical ariboflavinosis, in 5 of whom there were evidences of other types of deficiency disease. All 9 patients had cheilosis, 8 a characteristic glossitis, and 3 had seborrheic accumulation at the nasolabial folds. These patients' complaints varied from itching, burning and a sensation of roughness of the eyes with mild to severe photophobia with dimness of vision in poor light and partial blindness. In 8 patients injection of the conjunctiva on the lids and in the fornix was noted. This was accompanied in 5 by congestion of the bulbar conjunctiva with marked circumcorneal injection and gross opacities in the cornea. Slit-lamp studies revealed that the earliest change was a superficial invasion of the cornea by capillaries arising from the anterior ciliary vessels at the nasal and temporal sides of the cornea. Later the capillaries invaded the substantia propria and superficial and interstitial infiltration appeared. These corneal lesions were not benefited by nicotinic acid, thiamin, cevitamic acid, cod-liver oil, or crystalline vitamin A. However, riboflavin caused a regression of the lesions characterized by improvement in subjective symptoms, by diminution in size and occlusion of the capillaries, and by resolution of the superficial and interstitial infiltration. The ocular lesions were noted to recur upon discontinuance of the riboflavin therapy and to regress again upon its resumption. The authors stated also that in 2 patients with syphilis and interstitial keratitis in whom the keratitis was not improving under antisyphilitic treatment, considerable improvement resulted from the administration of riboflavin after antisyphilitic treatment had been discontinued. They thought that the beneficial effect of riboflavin therapy might be

due to the fact that riboflavin deficiency was the real cause of the keratitis and that the syphilis, if it played any part in the etiology, might be only an exciting factor. On the other hand, if syphilis itself were the cause of the keratitis, riboflavin deficiency might militate against the resisting and healing powers of the cornea.

In June, 1940, these same authors reported further observations on 47 patients known to be receiving insufficient riboflavin. The most frequent symptoms were found to be photophobia and diminution of vision not explained by the refractive error or by opacities in the media. The earliest and most common sign of ariboflavinosis was found to be circumcorneal injection due to congestion and proliferation of the limbic plexus. This was found in 45 patients. Actual invasion of the cornea by capillaries arising from the limbic plexus was observed in 37 patients; fine diffuse superficial opacities of the cornea were seen in 18; superficial punctate opacities in 2; interstitial nebulas in 6, and posterior punctate opacities in 2 patients. Vascularization of the cornea was seen to develop first just beneath the epithelium, later at varying depths in the substantia propria, and last just within the endothelium. Increased or abnormal pigmentation of the iris also was noted in 19 cases. This was seen to decrease during treatment. Photophobia, itching of the eyes, and congestion of the limbic plexus disappear usually within 48 hours after the administration of daily doses of 5 to 15 mg. of riboflavin. When extensive vascularization of the cornea had occurred, the time required to empty the vessels varied from 5 to 18 days. The authors believe that this form of dietary keratitis begins always as a superficial or subepithelial vascularization of the cornea, that superficial opacity is apt to follow, and that only later do the invading vessels penetrate the substantia propria. They are not apt to form a posterior plexus unless the deficiency is severe and prolonged. The vascularization of dietary keratitis is predominantly anterior while that of syphilitic keratitis is posterior; but, in the late stages, the two types of keratitis may be strikingly similar in appearance. The authors believe further that "ariboflavinosis is possibly the most prevalent, apparently uncomplicated avitaminosis; it is possible also that it is more easily recognized than others on account of the specific lesions of the eye which occur early in the period of deficiency."

Riboflavin in Rosacea and Other Forms of Keratitis. According to Doggart[4] in rosacea keratitis the cornea shows grayish-white infiltrates, chiefly involving the superficial layers of the substantia propria, with ill-defined margins and accompanied by large, freely anastomosing vessels continuous with those of the ocular conjunctiva. The epithelium overlying these infiltrates is often eroded so that corneal ulceration begins. Small rounded gray areas of opacity occur frequently in other parts of the cornea remote from the main lesion. Conjunctival vessels may encroach for a varying distance in the cornea all around its circumference. The lesions heal readily but also recur readily and the infiltration goes farther into the cornea with each recurrence. Verhoeff[15] calls attention to the similarity between rosacea keratitis, superficial punctate keratitis, and neuropathic herpetic-like lesions near the periphery of the cornea. It is of interest that according to both these

authors, writing in 1930 and 1915 respectively, improper diet and digestive disturbances are the most common causes of rosacea keratitis. Doggart adds hypochlorhydria and Verhoeff chronic alcoholism to the list of causes.

In May, 1940, Johnson and Eckardt[76] called attention to the similarity between rosacea keratitis and the corneal lesions in rats raised on a diet deficient in riboflavin. They treated 36 patients with rosacea keratitis by the addition of riboflavin to the diet. In 32, prompt healing of the corneal lesions took place and no recurrences occurred during the continuance of riboflavin therapy. Four patients responded slowly or not at all and failed to remain free from symptoms. Of the 36 studied, only 2 took adequate amounts of egg, liver and milk in their usual diet. These 2 did not respond to riboflavin therapy and were found to have no free hydrochloric acid in the gastric juice. Johnson and Eckardt had gastric analyses in 11 of their patients with rosacea keratitis. They found 6 of these had normal gastric acids but lived on a diet deficient in foods naturally rich in riboflavin; 2 patients who had adequate amounts of riboflavin in their diet had reduced gastric acids; 3 took a diet deficient in riboflavin and also had achlorhydria. They assumed, therefore, that rosacea keratitis might be a direct result of riboflavin deficiency and that it might develop either from the use of a diet deficient in riboflavin or from the inability to utilize the riboflavin supplied in an adequate diet because of the absence of free hydrochloric acid in the gastric juice or some other factor necessary for absorption.

With respect to the response of the lesions of rosacea keratitis to riboflavin therapy, Johnson and Eckardt state that acute solitary marginal infiltrates with minimal limbal vascularization disappear within 48 hours after intravenous injections of riboflavin or within 72 hours after oral administration has been started. Multiple marginal infiltrates on a site previously involved and more extensive infiltrates in the cornea respond more slowly. In such cases they advise during the first week 9 mg. of riboflavin intravenously daily or every other day. Then Elixir Vitamin B complex is given in amounts so that the daily intake of riboflavin is 3 mg. A diet containing more than the customary amounts of liver and milk is advised.

Johnson and Eckardt also treated a number of patients with active and inactive syphilitic interstitial keratitis for over a year with riboflavin orally, 6 to 9 mg. daily. They did not observe any dramatic disappearance of blood-vessels but thought originally that the response to treatment was satisfactory inasmuch as a far greater number of vessels than usual became empty of blood cells and could be seen only as empty channels with the slit-lamp. Later, however, they were discouraged with regard to the efficacy of this form of treatment when a girl 9 years of age, who had received 6 mg. of riboflavin daily for over 3 months, developed a severe interstitial keratitis in the other eye. They were unsuccessful also in an attempt to produce interstitial keratitis in rabbits infected with syphilis and placed on a diet deficient in riboflavin. These authors were inclined to consider the type of syphilitic keratitis reported by Kruse and his co-workers as responding excellently to riboflavin as a mixed dietary and syphilitic rather than a characteristic syphilitic keratitis.

However, Johnson and Eckardt again call attention to the importance of riboflavin in the metabolism of avascular tissues, like the cornea, in which Warburg's yellow enzyme is effective in transferring hydrogen from the tissue cells to the capillaries at the limbus. To be certain that an insufficiency of oxidative enzymes is not delaying healing they recommend vitamin B complex as supportive treatment in all forms of corneal ulcers. They note also that factors additional to riboflavin are essential to a healthy state of the cornea. They state that György observed that a deficiency of pantothenic acid in the diet of rats caused a high incidence of corneal ulcers which tended to progress to perforation and endophthalmitis. Addition of pantothenic acid to the diet is followed by a definite tendency to healing of these ulcers. Because of the inclusion of pantothenic acid in Elixir Vitamin B complex Johnson and Eckardt recommend this preparation in the treatment of ulcers of the cornea.

Johnson and Eckardt have been able to demonstrate demodecidae (face mites) in the expressed contents of meibomian glands in cases of acute multiple obstruction, the material being placed in a drop of cedar-wood oil or glycerin and viewed immediately under a low-power microscope. György[6] noted that pediculosis was encountered among experimental rats exclusively in the group fed diets deficient in riboflavin. Administration of riboflavin by mouth was found to cure the pediculosis. The authors suggest, therefore, that riboflavin may be of aid in the treatment of acute meibomitis.

Summary. As a summary, a statement from Sebrell may be quoted: "It therefore appears that at least some of the many cases of keratitis in this country of vague or unexplained etiology even without lip or tongue lesions are due to riboflavin deficiency. This work indicates that unrecognized riboflavin deficiency is perhaps very widespread in this country and is another indication of the probable extent of nutritional disease."

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF DECEMBER 17, 1940

Some Hitherto Unrecognized Excretion Products of Sulfapyridine and Their Relation to Urolithiasis. JOHN V. SCUDI and HARRY J. ROBINSON (Merck Institute for Therapeutic Research). The mechanism of the urinary elimination of sulfapyridine is more complex than has been postulated heretofore. A mono-hydroxyl derivative of sulfapyridine and its water soluble glucuronide have been isolated from dog urine (Scudi, J. V., *Science*, **91**, 486, 1940). These products are ordinarily measured by diazotization procedures as "free" or unchanged sulfapyridine.

The formation and excretion of these products has been studied in the rat (Scudi, J. V., and Robinson, H. J., AM. J. MED. SCI., in press). Following the administration of the drug there was an increased urinary output of glucuronic acid which indicated that as much as 40% of the "free" sulfapyridine was present as the highly soluble glucuronide. This was confirmed by a study of the ratio of free to acetylsulfapyridine, and a qualitative estimation of the urinary hydroxysulfapyridine.

The excretion of a part of the drug in a soluble form is important in the etiology of acetylsulfapyridine urolithiasis. If the body is deprived of the mechanism whereby this soluble product is formed, the body must detoxicate and eliminate larger amounts of the drug in some other fashion. Following liver damage induced by phosphorus poisoning the glucuronic acid output was no longer augmented by the administration of sulfapyridine. The production of the insoluble acetylsulfapyridine, however, was not depressed. Thus, three injections of phosphorus produced a 60% incidence of uroliths, whereas a control series of rats showed only a 10% incidence of stones at the sulfapyridine dose level studied.

Preliminary studies in man (Scudi, J. V., Ratish, H. D., and Bullowa, J. G. M., *Science*, **89**, 516, 1939), indicate that man and the rat employ the same mechanism for the excretion of sulfapyridine. Thus, liver function should be considered in the etiology of acetylsulfapyridine urolithiasis.

A Self Regulatory Duodenal Mechanism for Gastric Acid Control and an Explanation for the Pathologic Gastric Physiology in Duodenal Ulcer. HARRY SHAY and J. GERSHON-COHEN (Samuel S. Fels Medical Research Laboratory). By a direct approach in the human subject, we have demonstrated the presence in the normal duodenum of a mechanism which is brought into play by a concentration of acid peculiar to the individual. This concentration for any meal is represented by the peak of free acidity reached after the particular meal. When this concentration of acid reaches the duodenum a mechanism is activated that depresses gastric secretion and is responsible for the descending limb of the normal gastric curve.

In the failure of the normal response of such a mechanism, obtunded by the ulceration and inflammation produced by duodenal ulcer, we believe lies the explanation for the high acid extra-gastric curve seen in this disease. That such a failure of response does occur we have demonstrated in duodenal ulcer patients. If we combine our present findings regarding gastric secretion with the influence of the duodenum upon gastric motor function which we have previously described, we have for the first time, in the disturbance of one mechanism an explanation for the characteristic clinical gastric findings in uncomplicated duodenal ulcer—hyperperistalsis, hypertonicity, hypermotility and hypersecretion.

Reactions of Blood-vessels in Moat Chambers in Rabbits' Ears to Renin and Angiotonin. Richard G. Abell and Irvine H. Page (Department of Anatomy, University of Pennsylvania, and Lilly Laboratory for Clinical Research, Indianapolis City Hospital). Renin and angiotonin (Page, I. H., and Helmer, O. H. *J. Exp. Med.*, **71**, 29, 1940) were injected intravenously, and the effects upon small blood-vessels in transparent moat chambers in rabbits' ears observed with the microscope.

The injection of 0.2 cc. Ringer's solution was not followed by contraction of any of the vessels. The injection of 0.2 cc. renin was followed by arteriolar contraction. At the time of greatest contraction, 2.8 minutes after the injection, the arteriole photographed constricted to 0.24 its original diameter. The flow of blood through it was not interrupted. The injection of 1 cc. of angiotonin was followed by arteriolar contraction which became greatest 2.5 minutes after the injection. At this time the arteriole had constricted to 0.53 its original diameter. In this case also the flow of blood was not interrupted. No appreciable change in the diameters of the capillaries or venules was produced by either renin or angiotonin. The intravenous injection of 0.05, of 0.037, of 0.025 and of 0.012 mg. epinephrine was followed in each case by arteriolar contraction which stopped the blood flow in the vessels in the chamber.

Further experiments have been made using an angiotonin solution that had been standardized against epinephrine for equivalent blood pressure raising dosage. These indicate that the peripheral constrictor effect of angiotonin is from $\frac{1}{4}$ to $\frac{1}{2}$ as great as that of epinephrine.

Urinary Excretion of Pregnanediol Glucuronidate in the Hypertensive Disorders of Pregnancy. Bachman, C., Leekley, D., and Hirschmann, H. (Department of Obstetrics and Gynecology, University of Pennsylvania). The excretion of pregnanediol glucuronidate was investigated in 10 pregnant women who exhibited one or another of the following hypertensive disorders: 1, Pre-eclampsia; 2, mild, uncomplicated chronic hypertensi . e disease; and 3, severe chronic hypertensive disease complicated during gestation by the development of proteinuria. Output of this compound was abnormally low in the patients belonging

to the first and last of these groups, but was unaffected in those with uncomplicated chronic hypertension. Abnormal depression of excretion was first noted at the time that proteinuria appeared, and was continuously associated with the latter phenomenon during the remainder of gestation.

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